610.5
J86
L12

Vol. I JULY, 1916 No. 10

JUL 28 1916
UNIV. OF MICH. LIBRARY

The Journal of Laboratory and Clinical Medicine

VICTOR C. VAUGHAN, M.D., Editor-in-Chief
University of Michigan, Ann Arbor

ASSOCIATE EDITORS

Pharmacology
DENNIS E. JACKSON, M.D.
Washington University, St. Louis

Bacteriology
HANS ZINSSER, M.D.
Columbia University, New York

Immunology and Serology
FREDERICK P. GAY, M.D.
University of California, Berkeley

Physiological Pathology
PAUL G. WOOLLEY, M.D.
University of Cincinnati, Cincinnati

Physiological Chemistry and Clinical Physiology
J. J. R. MacLEOD, M.B.
Western Reserve University, Cleveland

ROY G. PEARCE, M.D.
University of Illinois, Chicago

Clinical Microscopy and Laboratory Technic
ROGER S. MORRIS, M.D.
University of Cincinnati, Cincinnati

Published by
THE C. V. MOSBY COMPANY
ST. LOUIS

$3.00 Per Annum Single Copies, 30 Cents

HAY FEVER PROPHYLAXIS.

Autumnal pollinosis (the ordinary hay fever of late summer and early fall) is held to be due to the pollen of ragweed, or to other pollens closely analogous to ragweed in their protein content.

An efficient immunizing agent in this type of hay fever is

RAGWEED POLLEN EXTRACT

The extract is administered hypodermatically.

We supply an accurately standardized product.

Ragweed Pollen Extract has given good results when administered after the onset of symptoms, but *the best effects are obtained by starting immunizing treatment a month or six weeks before the pollen season.*

For Fall Pollinosis—Immunize Now!

Each package of Ragweed Pollen Extract contains three 5-mil (5-Cc.) vials of 10 units, 100 units and 1000 units per mil (Cc.) respectively; one vial of physiological salt solution for use as a diluent, and one scarifier. When injecting, use any small syringe—preferably the so-called tuberculin syringe.

Full directions as to application and dosage accompany each package.

NOTE.—In packages corresponding to those of Ragweed Pollen Extract, we also market Timothy Pollen Extract for the treatment of spring pollinosis, and Pollen Extract Combined (Timothy and Ragweed) for treatment of individuals susceptible to both types of pollen.

LITERATURE SUPPLIED ON REQUEST.

Home Offices and Laboratories,
Detroit, Michigan.

Parke, Davis & Co.

The Journal of Laboratory and Clinical Medicine

VOL. I. ST. LOUIS, JULY, 1916 NO. 10.

ORIGINAL ARTICLES

THE SIMPLE INTERPRETATION OF POLYGRAPHIC TRACINGS*

BY EDWARD PERKINS CARTER, M.D., CLEVELAND, OHIO.

IT is to Mackenzie[1] that we are indebted for having applied the fundamental principles of the physiology of the circulation to the study of clinical cases, and for having devised, amidst the exigencies of an absorbing practice, the most satisfactory means for simultaneously recording the venous and arterial tracings.

The soundness of the graphic records in their application to cardiac pathology has been abundantly confirmed by animal experimentation and by the electro-cardiograph as originally developed by Einthoven and so brilliantly applied by Lewis.

FUNDAMENTAL PRINCIPLES.

The basis of the analysis of all polygraphic curves depends upon the *time relationship* between the events recorded in the venous and arterial tracings. Their accuracy, to within an utterly negligible factor of error, lies not in any given form or contour of the various waves upon the tracing, but solely upon the orderly or disorderly sequence of events as shown by an exact analysis by measurement from fixed points.

The venous pulse in the jugular vein is due entirely to changes in pressure occurring within the right auricle, and in order to interpret correctly our venous tracings one must have a clear understanding of the variations in pressure occurring within the auricle during the cardiac cycle.

As a result of experimental work with animals we know that graphic records obtained by sounds introduced through the veins into the right auricle always show first a wave directed upward, due to an increase in pressure within the auricle during auricular systole—the first positive wave. This wave ends shortly before the onset of ventricular systole and is followed by a slight drop in the tracing called the first negative wave. This depression is immediately followed by

*From the Medical Clinic of the Cleveland City Hospital and the Western Reserve University.

a second wave in an upward direction coincident with the onset of ventricular systole—the second positive wave, which in turn is followed by a conspicuous fall in the tracing—the second negative wave. Following this second fall there occurs a third wave in an upward direction, the sharp onset of which appears at a variable time after the second negative wave, the termination of this wave, however, occurs at a constant time interval after the second positive wave, its apex coinciding with the opening of the auriculo-ventricular valves which takes place but a fraction of a second after the closure of the aortic valves. This third wave in an upward direction is called the third positive wave.

Lewis[2] states that "its dependence upon a ventricular rather than upon an auricular event has been clearly established experimentally and clinically." * * * "That the rise of pressure in the auricle due to ventricular systole is a factor of great importance." * * * "That it has been associated also with the sudden release of the base of the ventricle at the commencement of ventricular diastole." * * * "It is probable that both factors play a part in the production of the wave under certain circumstances."

The fact, however, that its production is essentially due to the rise in venous pressure in the right auricle as this chamber fills during diastole, the end of its rise terminating abruptly with the opening of the auriculo-ventricular valves, makes it difficult to interpret this wave as *positive* in the sense of that term as applied to the first two positive waves.

Following this third wave in an upward direction there succeeds the third negative wave coincident with ventricular diastole.

METHOD OF PROCEDURE.

To obtain satisfactory venous tracings from clinical cases the jugular tambour of the Mackenzie ink polygraph, or a small thistle funnel in its stead, should be placed over the jugular bulb, on the right side of the neck, at a point a little above and about an inch to the right of the sterno-clavicular joint. When possible the patient is placed in a horizontal position, the head being slightly elevated and the muscles of the neck relaxed. When it is not possible to place the individual flat one must adapt his procedure to the exigencies of the case. We may place the tambour at a higher level, or may often succeed in getting satisfactory tracings from the left side when only failure results from adopting the customary right side. The radial tambour should be connected to that pen or writing lever nearest the patient.

In a normal jugular tracing a regularly recurring series of waves is recorded grouped together in sequences of three more or less conspicuous summits with a fall in the tracing between them, a slightly longer pause occurring between the third wave of each group and the first wave of the following group. (See Fig. 2,A.) These three waves have been named "a," "c" and "v," these letters indicating the origin of the waves.

"a" The first positive wave.
"x" The first negative wave.
"c" The second positive wave.
"x" The second negative wave.
"v" The third positive wave.
"y" The third negative wave.

The "a" wave is due to auricular systole. Under certain conditions, referred to below, the "a" wave may be absent from the venous tracing.

The "a" wave and the following depression, measured from the onset of "a" to the onset of the "c" wave have a duration of from .1 to .2 seconds. This constitutes the so-called "a-c" interval, and represents the time which elapses between the onset of auricular and ventricular systole.

Whatever may be the exact production of the "c" wave its dependence upon ventricular systole has been established, and the occurrence of the "c" wave in the venous tracing synchronous with the appearance of the carotid pulse in the neck makes it the most important wave in our analysis and gives us a fixed standard upon which the correct interpretation of all tracings depends. Any increase in the "a-c" interval over .2 seconds is regarded as pathological, constituting delayed conduction, or a slight degree of heart-block.

The onset of the "v" wave varies under different conditions, its termination however corresponds exactly with the opening of the tricuspid valves and occurs at an interval of approximately .4 seconds after the onset of the "c" wave. It not infrequently happens that the "v" wave is split, a fact considered by Lewis as affording evidence of the double factors in its production.

It is upon the recognition and time relationship of these three waves as determined by comparative measurements upon the arterial tracing that the accuracy of an analysis of the venous curve depends.

THE ARTERIAL SPHYGMOGRAM.

In any analysis of an irregularity of the heart we must determine whether or not there is present a *dominant rhythm*. By this term is meant that fundamental physiological rhythm which arising at the sino-auricular node controls the heart beat. Under normal conditions this dominant rhythm originates the cardiac response at a uniform rate of 72-76 to the minute. It should be recalled, however, that the normal impulse arising at the sino-auricular node is subject to wide variations in rate, ranging from 32 to 100 or above a minute.

This dominant rhythm may be modified in various ways, as follows:

1. Physiological variations caused by an increase in the rate of stimulus production at the pacemaker.

a. These are met with essentially as an increase in rate due to stimulation of the sympathetic, or to factors interfering with vagus inhibition.

b. Slowing of the normal rate from vagus stimulation or irritation.

c. Certain so-called phasic variations attributed to the action of the vagus; seen conspicuously in children as changes in rate with in- and ex-piration.

2. Pathological variations caused by,

a. Abnormal impulses arising elsewhere than at the sino-auricular node, called ectopic.

b. By interference with, or complete interruption of the passage of the normal impulse from auricle to ventricle.

We establish the presence of a dominant rhythm by the regularly recurring incidence of beats at points which are equal distances apart, or by demonstrating that the apparently irregular longer spaces appearing in a tracing are but simple multiples of the shorter beats which represent the dominant rhythm. This is spoken of as the "spacing" of the arterial curve. When there is no evidence of

a dominant rhythm present in a tracing, when that is the beats are all of varying lengths without any periodic slowing or quickening of the pulse rate, when no two phases of irregularity are identical in duration and it cannot be proven that the long intervals are simple multiples of the short beats, then the pulse is said to be totally irregular.

THE ANALYSIS OF THE VENOUS CURVE.

We determine first that wave in the jugular tracing occurring synchronously with the carotid pulse. We know that the radial wave at the wrist occurs .1 of a second after the carotid wave in the neck, and this fact gives us the means by which we can determine the "c" wave in the venous tracing.

With the jugular and radial tambours in place run off a short strip of venous tracing, then without moving the jugular tambour, stop the polygraph making an ordinate upon the paper by moving the pens quickly from side to side—these ordinates are called index marks; now without having shifted the position of the jugular tambour apply firmer pressure and secure a short strip of carotid tracing, making similar index marks upon stopping the instrument. We now have two tracings, venous and carotid together with the radial, upon which we can determine accurately by measurement the time relationship of the events occurring in

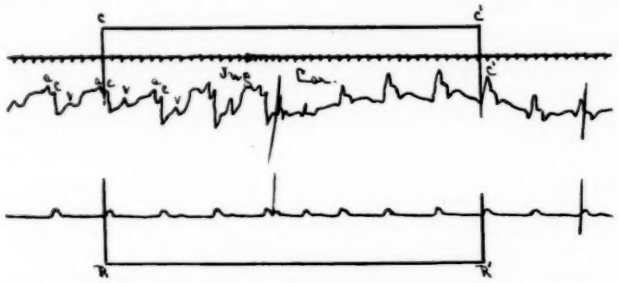


Fig. 1.—To illustrate the method of determining the "c" wave in the jugular tracing. Both jugular and carotid tracing taken without moving the jugular tambour.

the jugular and carotid tracing to the up-stroke of the corresponding radial. All measurements being made from the index marks at the right on to the tracing at the left.

We establish first the carotid up-stroke C′ corresponding to a given radial wave at the right of the tracing; we then measure off an equivalent number of beats on the radial tracing on the venous side at the left, we may call this distance R-R′.

If we now transfer this measurement R-R′ to the upper tracing placing the point corresponding to R′ at C′, a vertical line from R will fall upon a wave in the jugular tracing which bears the same relationship to the up-stroke of its corresponding radial wave R as does C′ to R′, this wave therefore is the "c" wave and we may mark it as such. This procedure can be applied only when the polygraph is running at the same rate in both venous and carotid tracings, and we must be sure that the instrument when started after being stopped has developed the top speed at which it is set. The time marker in all tracings records fifths (1/5) of a second.

In routine work this method of procedure is unnecessary. We simply meas-

ure the distance from the index mark at the right to the up-stroke of any given radial wave. Transfer this measurement to the time-marker tracing, lengthen it by one-half of the distance between any two points, i.e., by one-tenth (1/10) of a second, then transferring this measurement to the jugular tracing place one end upon the index mark and the other will fall upon the up-stroke of the "c" wave. In this way determine three or more "c" waves.

THE FIXATION OF THE "A" WAVE.

We next determine the "a" wave by locating that wave which recurs at a constant interval immediately before "c." In the normal jugular curve the "a" wave is found at a period slightly less or just equal to the distance between any two points on the time marker, i.e., at a point slightly under or exactly equivalent to one-fifth (1/5) of a second before the onset of "c." In a given tracing in which the "a" waves recur with normal regularity in their time relationship to "c" they will be seen to have essentially the same form from one cardiac cycle to the next, in some instances altered slightly with recurring regularity by the respiratory rhythm.

It is important to note the contour of the "a" waves in any given instance, for under some conditions it is by the comparison of such regularly recurring waves which space exactly that we are able to assign the origin of the wave in question to auricular systole. This is of the utmost importance in those instances in which there are additional "a" waves present having no relation to any corresponding "c" wave.

While this statement holds true for any large number of observations, there are, of course, many occasions when the "a" wave coinciding with a "c" or a "v" wave is greatly obscured and its location in the tracing must be determined by careful spacing from the established "a" waves present.

THE FIXATION OF THE "V" WAVE.

In the normal jugular tracing the "v" wave usually appears as a conspicuous peak at a constant interval after "c." For this reason it is an important landmark in the jugular curve and by virtue of its time relation to the preceding "c" is of great value in the analysis of all tracings.

As stated above the onset of the "v" wave is variable, its apex on the other hand coincides with the opening of the tricuspid valves and will be found to occur at approximately .3 of a second after the apex of "c." Having determined the "c" wave it is usually not difficult to fix the apex of the succeeding "v" wave in its relation to the preceding "c" and to the dicrotic notch in the radial. When the "v" wave is split appearing as two small waves or as a single wave with a bifurcated peak one must proceed cautiously eliminating any possibility of confusion from a supernumerary "a" wave, and must further show that the "c" wave and the split wave immediately following fall within the sphygmic period of the arterial tracing. The sphygmic period is the period of ventricular systole. If we measure the distance in the venous tracing from the onset of the "c" wave to the beginning of the drop in "v" (lines 3 to 5, Fig. 2,A) and transfer this measurement to the radial tracing, making an allowance of one-tenth (1/10) of a second for the difference in time between the carotid and the radial, we shall

find that our measurement will fall one-tenth of a second before the up-stroke of the radial and at the base of the dicrotic notch.

It often happens that the "v" wave does not appear as a conspicuous peak, being frequently masked by the succeeding "a" wave. Any increase in the speed of the heart is accomplished at a sacrifice of the diastolic period, hence not infrequently when the heart's rate is enhanced "v" and "a" may be fused.

THE VENTRICULAR VENOUS PULSE.

Under certain conditions no "a" waves can be found in the jugular tracing while the heart's action may be regular or irregular. This type of venous curve has been called the ventricular form of venous pulse. When the pulse is regular the absence of "a" waves from the venous curve may be due to:

1. Overfilling and distension of the right auricle, following greatly increased pressure on the right side of the heart.

2. When the cardiac rate is increased and the "a" wave falls back upon the preceding "v."

3. Rarely in the presence of a slow pulse rate (36-42) due to the existence of complete articulo-ventricular dissociation (complete heart-block) associated with auricular fibrillation.

When the pulse is irregular the absence of "a" waves from the venous tracing signifies *auricular fibrillation.*

This form of venous pulse is most commonly seen as a result of the latter condition. In addition to the absence of all "a" waves it is further characterized by the fact that all the conspicuous waves in the tracing lie within the sphygmic period. The general shape of the waves in the ventricular venous pulse tracing may vary widely from case to case, but no matter how great this variation in form the conspicuous summits will be found to occur during systole. The so-called plateau type is perhaps the commonest form met with. (See Fig. 13,B.)

OTHER WAVES OCCURRING UPON THE VENOUS CURVE.

Under certain conditions additional waves are met with in the jugular tracing. These extra jugular waves will be found during the long diastolic pauses when the heart's rate is slow. The origin of these may be attributed to three sources:

1. The second onflow wave appearing as a gradual rise in the venous curve during diastole. Due to distension of the veins when the heart is already filled, or to the gradual increase in pressure in the veins and heart during the venous filling.

2. A small wave appearing in mid diastole having a definite time relationship to the preceding "v," seen conspicuously with a very slow heart rate. This is called the "G" or the "H" wave, having been described independently by Gibson[3] and Hirschfelder[4] and attributed by these observers to "the snapping together of the auriculo-ventricular cusps at the end of ventricular filling."

3. In certain instances of auricular fibrillation when the heart's rate is slow irregular undulations due to the rapid and imperfect partial contractions of the auricle may be seen. These are called fibrillation or "f" waves.

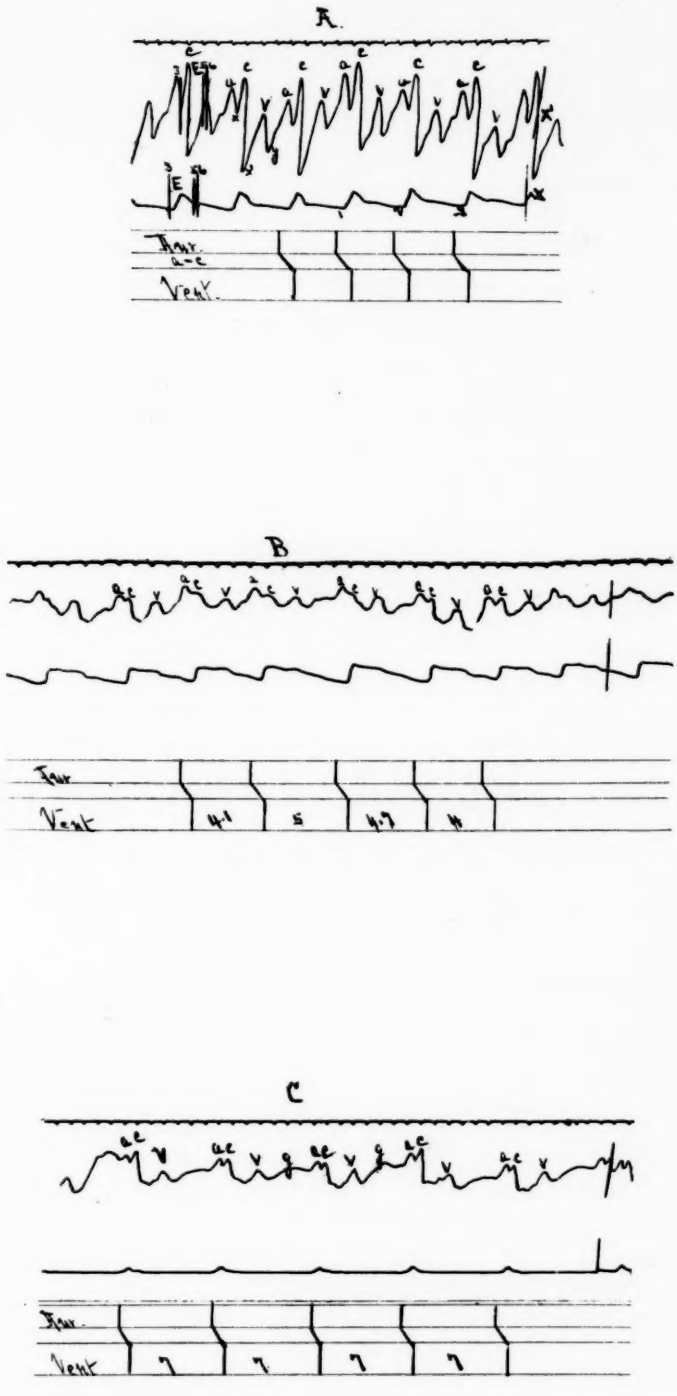


Fig. 2.—A. Normal jugular tracing. 3 to 5 sphygmic period. At 6 the tricuspid valves open. "a," "c," "y" and "x," "x'" and "y" the positive and negative waves.
B. Sinus arrhythmia.
C. Sinus bradycardia. Pulse rate 52 to the minute.

SUMMATION OF WAVES.

Whenever any two waves in the jugular curve coincide it is spoken of as a "summation." Not infrequently we see this summation of waves when the heart's action is perfectly regular though the rate is increased. In the sense of the term however in which it is commonly used it is applicable essentially to those instances of summation resulting from some disturbance of the normal mechanism.

We may find an "a" wave superimposed upon a "c" or upon a "v" wave; or a "c" wave upon "v" or "a." When this summation occurs the combination of "a" and "c" is usually more conspicuous than is that of "a" and "v" or "c" and "v." There are of course exceptions to this statement.

THE SIGNIFICANCE OF DELAYED CONDUCTION.

It is utterly unessential to the purpose in view to discuss in any detail our knowledge of the origin of the contraction impulse and its spread from auricle to ventricle.

We know that in the presence of a delay in the conduction time there oc-

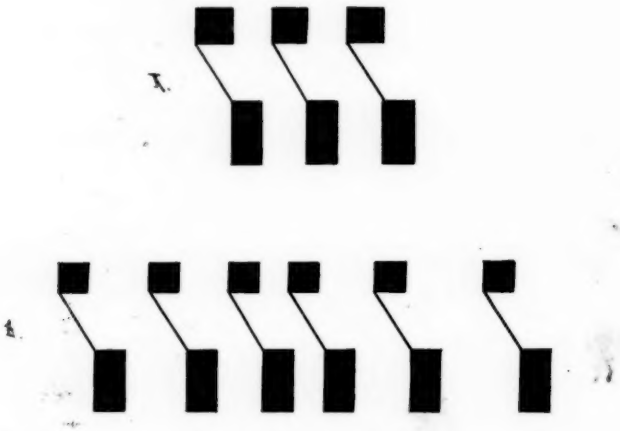


Fig. 3.—A. Diagram illustrating the normal mechanism.
B. Diagram illustrating a sinus arrhythmia.
In this and in all similar diagrams the upper squares represent auricular systole, the lower rectangles ventricular systole and the line uniting the two the conduction time, or a-c interval.

curs a change in the time relationship of the events taking place in the heart graphically portrayed in the jugular curve as a lengthening of slight or greater degree in the "a-c" interval. This constitutes the first degree of heart-block.

In the presence of the failure of the auriculo-ventricular bundle to convey the normal impulse from the pacemaker we find an isolated "a" wave, or with any of the higher degrees of heart-block alternately isolated "a" waves while in complete heart-block we can space the regularly recurring "a" waves and show that they have no constant time relationship to the "c" waves.

Depending upon the extent of impairment of conduction in a given instance there may be a considerable variation in the "a-c" interval present in a given case. This is particularly true of the higher degrees of heart-block in which we often find a rhythm of ventricular response varying between a 2:1, 3:1 and 4:1 ratio. In the simpler states in which there is present an occasional failure of conduc-

tion, spoken of as a dropped beat the first delay in the "a-c" interval exceeds the normal conduction time by a slightly longer duration than the second prolonged interval—occurring just before the dropped beat—exceeds the first. Immediately following the dropped beat the conduction time is again shortened.

Following the classification of Lewis[5] we may consider in detail the simple interpretation of the common arrhythmias of the heart.

If in Fig. 2,A we measure the distance from the index mark "x" on the right to the up-stroke of the radial marked "1" add one-tenth of a second to this measurement and transfer it to the jugular tracing placing one end on the index mark "x'," the other end will fall upon the up-stroke of "c." Repeating this for "2" and "3," we then proceed to fix the "a" and the "v" waves, showing that they space equally and occur at a constant time interval in relation to "c;" "a" at slightly less than .2 sec. before, and the apex of "v" at .4 sec. after the onset of "c." The fall in pressure in the "v" wave will be found to occur at approximately .3 sec. after the fall in "c." This measurement may be used in obscure curves.

The further method of analysis is shown beneath the tracing, the upper row of vertical lines representing auricular, the lower ventricular systole, the line joining the two indicates the conduction time or "a-c" interval. These vertical lines are drawn at points corresponding to the onset of "a" and "c." It must be remembered that as the pens write in an arc of a circle all measurements must be made from the index mark at the right on to a line parallel with it at any given point and when possible at the same level.

The three negative waves are marked x, x' and y. The period E between the lines 3 to 5 corresponds to the sphygmic period. The measurements in the analysis beneath the tracing represent fifths of a second and fractions thereof, easily obtained from the time marker tracing. The diagram below illustrates the conventional method used to portray the sequence of events taking place in the cardiac cycle. The upper small squares represent auricular, the lower rectangles ventricular systole. The line uniting the two by its acuteness or obtuseness indicates the normal or a prolonged conduction time.

SINUS ARRHYTHMIA.

Whenever as in Fig. 2,B there is a pronounced irregularity of the radial tracing we must determine whether the arrhythmia is due to disturbances affecting the sinus rate, the so-called respiratory and phasic arrhythmias of vagus origin, or to definite pathological changes in the orderly sequence of events.

Proceeding with our analysis, we note that the "a," "c" and "v" waves occur with the usual time relationship to each other. There is no delay in conduction time, the "a-c" interval measuring less than 1/5 sec. There are no extra "a" waves present and there is no evidence of the occurrence of premature beats. There is, however, a difference in the length of the diastolic pauses due to the variation in rate at which the contraction impulse is set free.

SINUS BRAYCARDIA.

In the presence of a slow and regular pulse rate as in Fig. 2,C the possibility of a certain degree of heart-block must be kept in mind. This is excluded by the absence of any disturbance in the orderly spacing of the three "a,"

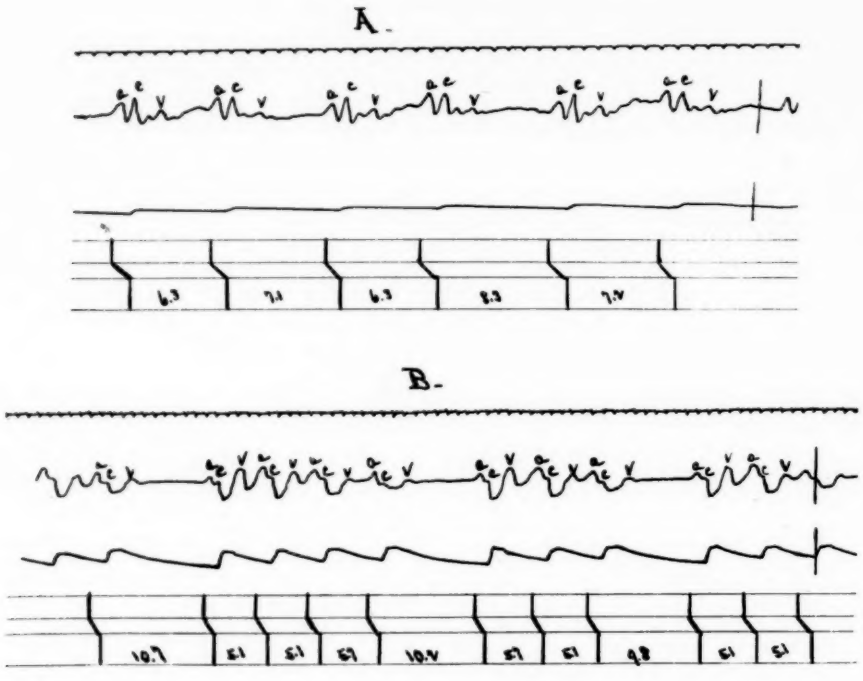


Fig. 4.—A. Marked sinus bradycardia, together with sinus arrhythmia. Pulse rate 38 to the minute. No delay in conduction time. Confirmed by electrocardiograph. B. Interpreted as sino-auricular block, associated with sinus slowing and arrhythmia. Pulse rate 58 to the minute. Confirmed by electrocardiograph.

"c" and "v" waves. The "a-c" interval measures less than 1/5 of a second. There are no extra "a" waves present. Note the conspicuous rise in mid-diastole that may possibly be regarded as a "g" wave. There is no marked arrhythmia. We have to do with a simple sinus slowing.

In the instance illustrated in Fig. 4,A, we are dealing with an extreme degree of sinus slowing together with a sinus bradycardia. The "a-c" interval measures a full 1/5 sec. Confirmed by the electrocardiograph. Note the split "v." There is no disturbance in the orderly sequence of "a," "c" and "v."

SINO-AURICULAR BLOCK.

Whenever an apparently regular pulse is interrupted by pauses of considerably greater length than the normal interval between beats, the disturbance is commonly due to a premature beat which fails to carry through to the wrist, or to the failure of ventricular response giving rise to a dropped beat. The long pauses seen in the tracing in Fig. 4,B are due to an entirely different cause.

This tracing confirmed by electrocardiographic study has been interpreted as illustrating a true so-called sino-auricular block. There are no additional "a" waves present during the long pause in the jugular curve and there is no disturbance in the time relationship of "a," "c" and "v." The dominant rhythm in this bit of tracing and in additional long records spaces at 5.1. The first long pause at the left in the tracing measures 10.7, the second 10.2 just double the time of two beats of the dominant rhythm, and the third 9.8. The average dura-

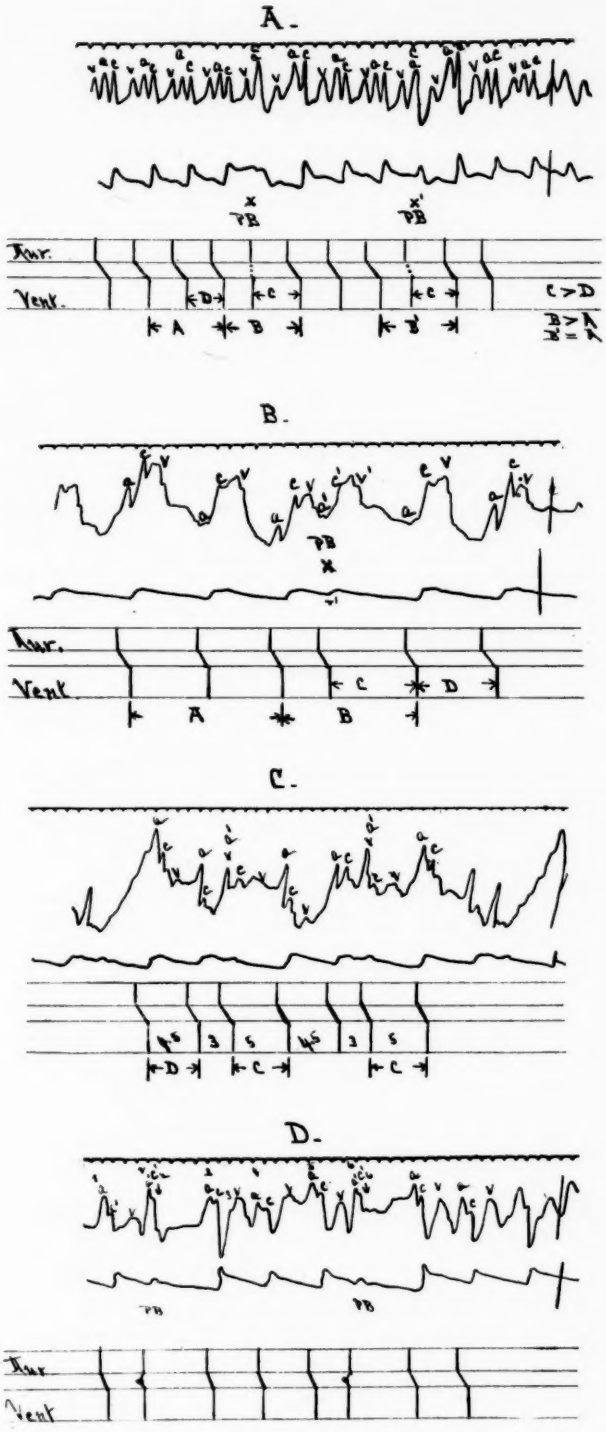


Fig. 5.—A. Premature beats ventricular in origin.
B. Premature beats auricular in origin.
C. Multiple premature beats, auricular in origin.
D. Premature beats, possibly nodal in origin.

tion of the long pauses in many additional records measured 10.2 exactly twice the time of the dominant rhythm.

For some cause, at these long pauses, the formation of stimulus production takes twice the time normal for this individual.

PREMATURE BEATS.

When the normal rhythm is disturbed by one or more such irregularities as appear in Fig. 5,A the clue to the cause of the disturbance is at once suggested by analysis of the radial tracing alone and readily confirmed by a comparative analysis of the jugular and radial curve.

In this jugular tracing the "a" waves will be found to space regularly throughout. The "c" waves space regularly up to the point of disturbance marked x. At this point there occurs a premature contraction arising in the ventricle and the "c" wave corresponding to the accompanying radial coincides with an "a" wave, which occurring at its expected time finds the ventricle in a refractory state. Following this premature contraction there is a pause in the radial tracing longer than the time of one normal beat. This is called the "compensatory pause."

The period C is longer than D. With the first premature beat marked x, the period of disturbance—that period including the premature beat and the normal beat immediately preceding it—is slightly greater than the distance between two normal beats. With the second premature beat x′ the period of disturbance B′ is exactly equal to A. The reason for this compensatory pause is made clear in the accompanying diagram (Fig. 7,A). The premature contraction arises in the ventricle. The next ventricular response must wait for the next auricular systole. Note the absence of any disturbance of auricular rhythm, also the effect of the summation of "a" and "c."

When the premature contraction arising in the ventricle is so weak that it does not carry through to the radial, we have a pause in the radial curve equal to twice the time between two normal beats. A similar pause may be due to other causes. (See Figs. 4,B and 11,B.)

When following an irregularity in the normal rhythm the period of disturbance measures less than the distance between two normal beats and the compensatory pause C is longer than one normal beat, the premature contraction arises in the auricle.

In Fig. 5,B the "a" waves space up to the time of the disturbance. At this point the normal rhythm is interrupted by a premature beat marked x. We find "c‴" in relation to its corresponding radial wave r′, and just before it, with the normal time relation, the "a" wave of the premature auricular contraction marked "a‴" in the figure. Following this premature contraction arising in the auricle there is a slight disturbance in the subsequent auricular rhythm and the appearance of the next "a" wave is a little delayed. Note that the period of disturbance B is less than A, while the compensatory pause C is longer than D.

When the normal rhythm is disturbed by multiple premature beats as in Fig. 5,C, and the compensatory pauses, or "end" pauses, are all of the same length the premature contractions are of auricular origin, excepting only that rare condition when the premature contraction may originate in the junctional tissues.

It occasionally happens, as in Fig. 5,D, that it is extremely difficult to de-

termine by the polygraph alone whether the premature contraction arose in the auricle or in the junctional tissue. In the above figure "a^2" and "a^6" marked a′ occur prematurely, by a short interval. "C^2" and "c^6" also occur prematurely and coincide with "a^2" and "a^6." The synchronous onset of "a" and "c" prematurely can only result from an impulse arising in the junctional tissue at the A-V node. The above tracing may possibly be regarded as illustrating premature contractions nodal in origin.

Whenever an irregularity repeats itself and the measurement of one cycle of the arrhythmia can be superimposed accurately upon a similar cycle appearing elsewhere in the tracing, the irregularity may be due to: (a) premature con-

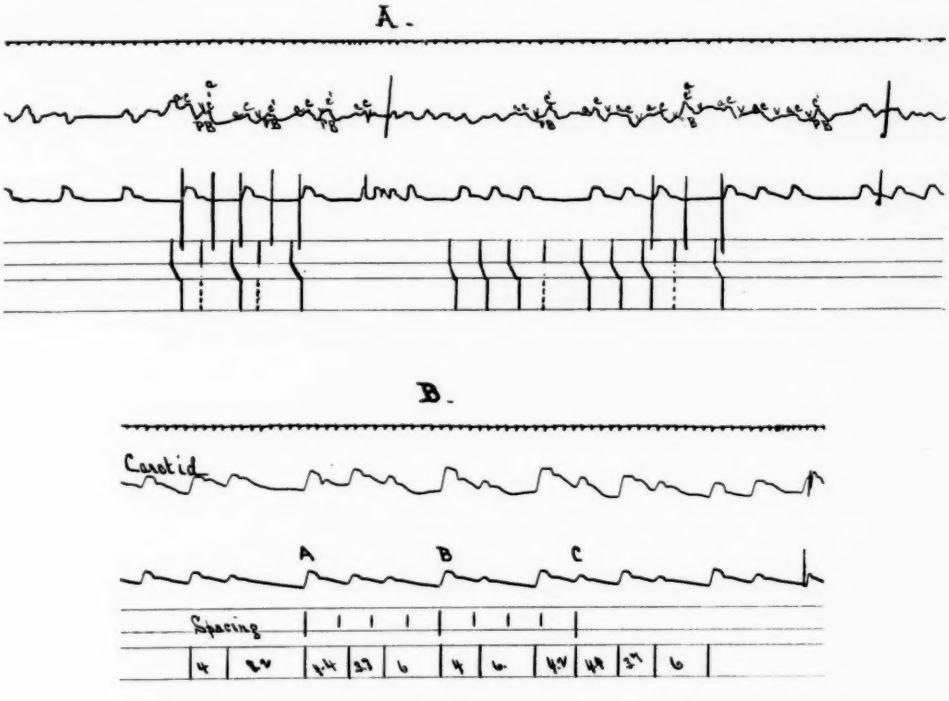


Fig. 6.—A. A regular irregularity due to premature beats ventricular in origin.
B. An irregularity due to premature beats ventricular in origin.

tractions ventricular or auricular, (b) to the occasional occurrence of dropped beats, or (c) to the presence of a high degree of heart-block with a wide variation in the ventricular response. No matter how irregular such a tracing may appear, if the irregularity repeats itself, or the radial can be spaced it cannot be due to auricular fibrillation.

Fig. 6,A illustrates a regular pulse alternating between a rhythm one-half the normal rate and a trigeminal pulse. The long pauses are twice the length of the short. The tracing can be spaced. It is due to premature contractions arising in the ventricle too weak to affect the radial.

In Fig. 6,B we have a type of irregularity frequently confusing. On careful measurement there is a wide variation in the length of the individual beats in the radial curve, and yet this tracing can be spaced. The period from A to

B equals that from B to C. The distance A-B and B-C is but a multiple of the shortest interval 3.7. In spite of the gross irregularity the pulse is not totally irregular. It is due to premature contractions arising in the ventricle.

PAROXYSMAL TACHYCARDIA.

When with a regular pulse the rate is altered abruptly, the change may be due to one of three causes.

If the change in rate bears a definite ratio to the previous rhythm and the pulse rate is exactly halved, the slow rate may be due to either premature ventricular contractions which do not reach the radial, or to the sudden development of a 2:1 heart block. When there is no exact ratio between the slow and the rapid rate the change is due to the sudden onset, or offset, of a paroxysmal tachycardia.

Fig. 8,A illustrates two short attacks of paroxysmal tachycardia. After a similar preceding paroxysm there was a return to the normal mechanism for one

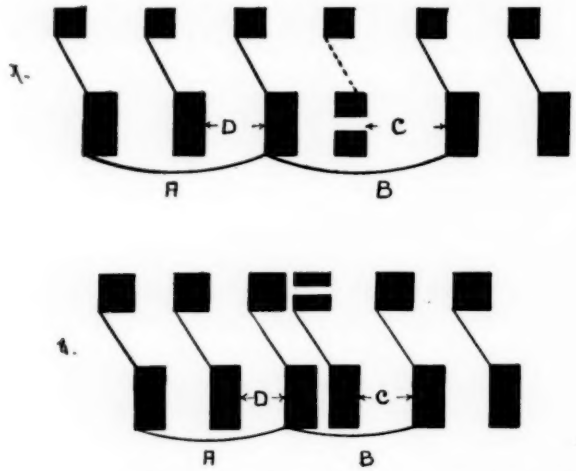


Fig. 7.—A. Diagram illustrating the reason for the disturbance in premature ventricular contractions. Note that C is greater than D, and that B equals A.

B. Illustrates the reason for the disturbance in premature auricular contractions. Note that C is greater than D, but that B is less than A. The split rectangle and square represent a premature contraction in this and all similar diagrams.

beat. At x another paroxysm onsets abruptly, the first beat of the new rhythm following a premature auricular contraction. The disturbance lasts for seven beats, there is a return to the dominant rhythm for one beat which in turn is again followed by a paroxysmal cycle lasting for seven beats. In long tracings from this case the attacks varied from seven to twenty beats. Such attacks may last from a few minutes to hours or even days. In the analysis of the jugular tracing the clue to "a," which after the first premature contraction falls with "v," is found in the initial beat of the new rhythm. Note that the end pauses are equal and that A equals B.

HEART-BLOCK.

When we can show in the jugular tracing that the "a-c" interval exceeds one-fifth of a second, it is evidence that there exists a delay in the conduction time.

This condition is called the first stage of heart-block. In Fig. 9,A, the "a-c" interval measures 1.2 fifths, exceeding slightly the normal of .2 seconds. This tracing also shows two premature auricular contractions.

When there is an occasional failure of the ventricle to respond to the impulse coming from the auricle it is called the second stage of heart-block or the stage of dropped beats. Fig. 9,B illustrates the occurrence of dropped beats. Note the prolongation of the conduction time up to the point of failure of the ventricular response. Note that the period B measures less than A.

In complete heart-block the analysis of the tracing is carried out in the usual way. Having determined "c" we may proceed to fix "v." We are at once struck by the variation in the general outline of "v." We then see that there is no wave present having the constant time relation of "a" to "c," but find a series of *regularly recurring* waves falling either before, with or after "c" and "v" in an apparently utterly haphazard relation to these two waves.

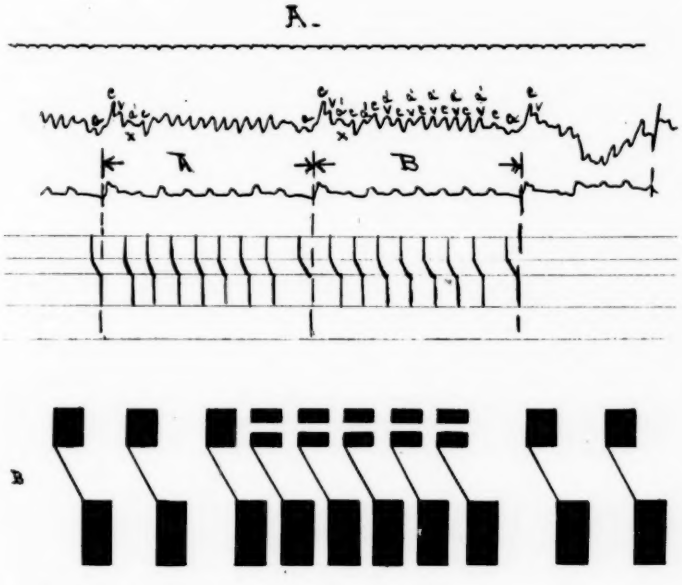


Fig. 8.—A. Paroxysmal tachycardia.
B. Diagram illustrating the nature of the disturbance in paroxysmal tachycardia.

The only possible source of a regularly recurring wave in the jugular curve at a higher rate of speed than "c" is auricular systole; if therefore these peaks can be shown to space accurately they are "a" waves. Note the difference in the summation of "a" and "c" and "a" and "v" in Fig. 9,C.

AURICULAR FLUTTER.

Although the polygraphic records of auricular flutter are often difficult to interpret, there are many instances in which the analysis is so simple that there should not be the slightest question as to the nature of the disturbance, while without them or without electrocardiographic records the diagnosis is impossible.

The jugular curve falls briefly into two types: one made up of a sequence

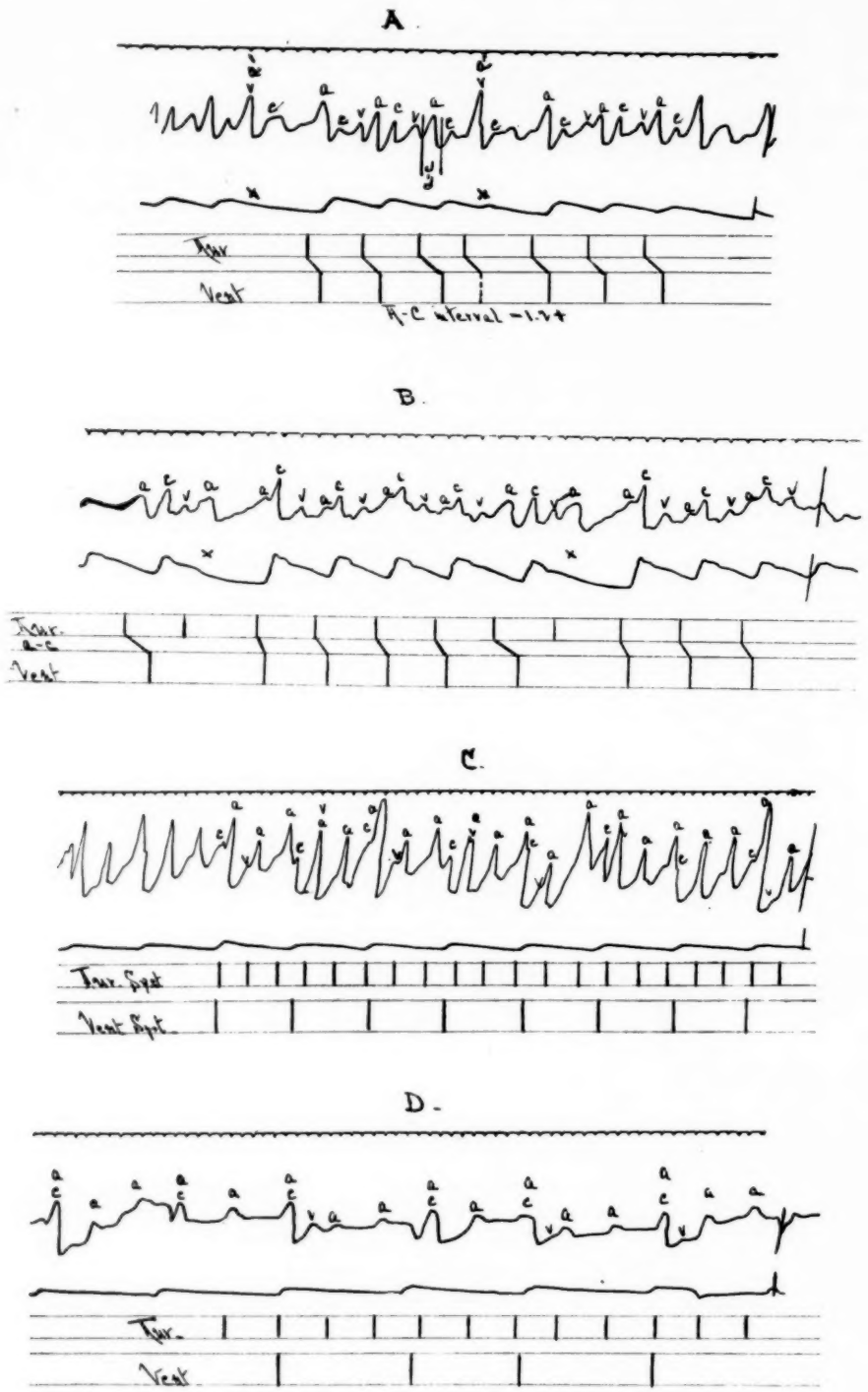


Fig. 9.—A. Delayed conduction time. A-C interval measures more than .2 seconds. First stage of heart-block.
B. Dropped beats. Second stage of heart-block.
C. Complete A-V dissociation. Complete heart-block. Pulse rate 38 to the minute.
D. Complete heart-block. Pulse rate 32 to the minute.

of rapid more or less uniform waves, the other appearing as paired waves with a constant time interval between the pairs. The pulse may be regular or irregular. Whenever there is present in the jugular tracing a regularly recurring sequence of waves, which space accurately from one cycle to the next, occurring at a rate higher than normal, with or without conspicuous summation auricular flutter should be suspected.

In Fig. 11,A, a tracing from a young individual with auricular flutter, the interpretation is evident. Note the conspicuous summation of "a" and "c." The distance A when transferred to any part of the jugular curve will include eight "a" waves. The ratio of ventricular response in this case was almost constantly 4:1.

In Fig. 11,B the analysis is more difficult. The radial tracing shows an irregularity, and the waves in the jugular curve are not conspicuous, though on close inspection a slight summation of "a" and "c" and "a" and "v" can be made out. A clue to the correct interpretation in this tracing is found in the regu-

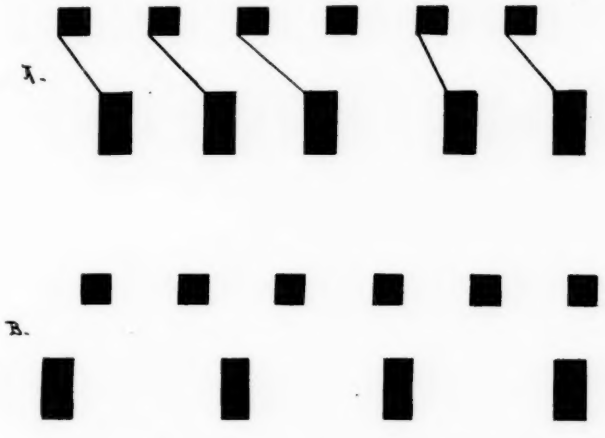


Fig. 10.—A. Diagram illustrating delayed conduction time and a single dropped beat.
B. Diagram illustrating complete A-V dissociation.

lar irregularity of the radial, the long intervals are exactly twice the length of the short. (See above for other causes of similar long pauses.) This fact together with the analysis of the jugular curve makes the interpretation simple. A given measurement on the radial tracing if transferred to any part of the jugular curve will include the same number of waves—auricular systole. In this tracing the period A, three long pauses, equals the period B, two long and two short pauses, and includes twelve "a" waves or auricular systoles.

When as sometimes happens we have an even more irregular response on the part of the ventricle we proceed in the same way to space the curve. In Fig. 11,C (from the same case) at the left of the tracing the ratio of ventricular response varied from 4:1, 3:1, 5:1. Here the distance A, 11 auricular systoles, equals the distance B, also 11 auricular systoles. At the time when this latter tracing was taken the predominant ratio of ventricular response was, however, 3:1. Note the summation of "a" and "c," and "a" and "v," and the constant time relationship of the paired waves, also that every third "a" wave lies buried

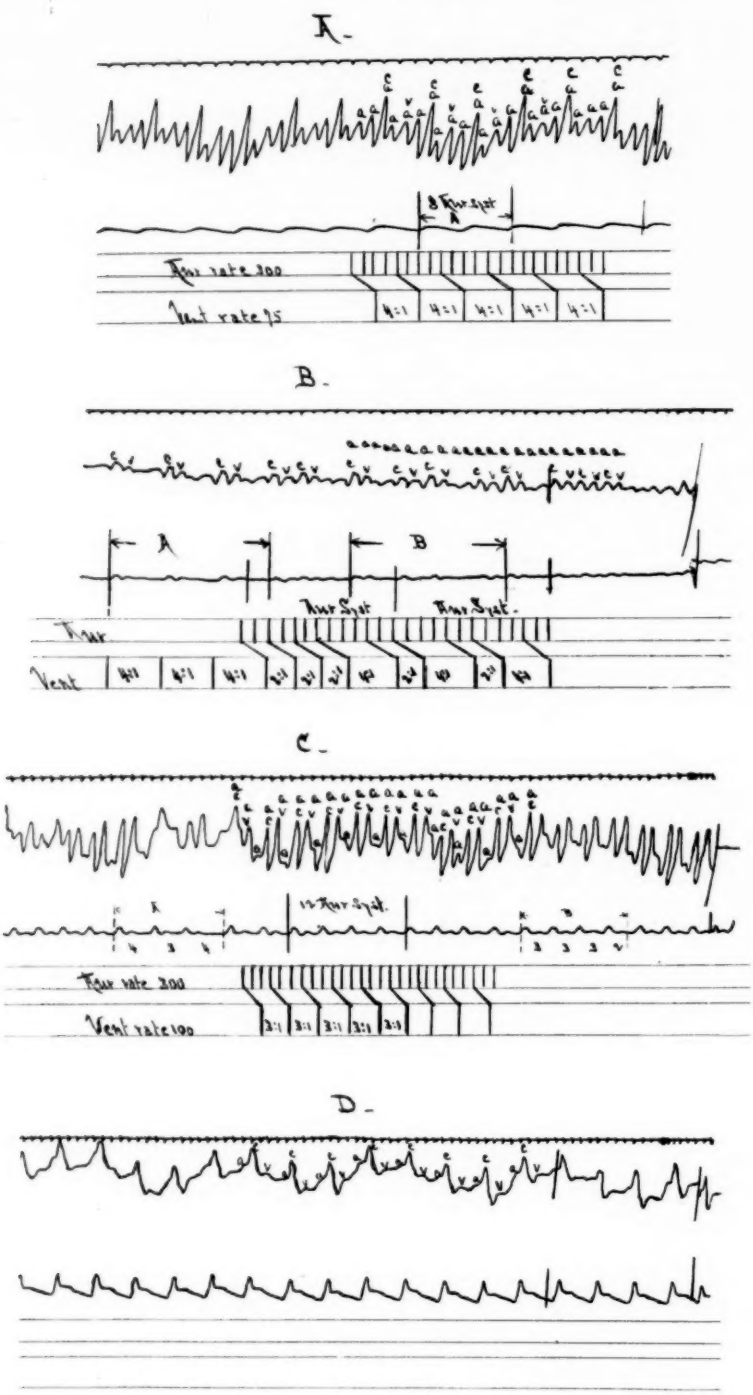


Fig. 11.—A. Auricular Flutter. Auricular rate 300, ventricular rate 75 to the minute.
B. Auricular Flutter. Auricular rate 300, ventricular rate varied from 82 to 98 to the minute.
C. Auricular Flutter. Auricular rate 300, ventricular rate 100 to the minute.
D. Tracing from the same individual as B and C.
Return to the normal rhythm following digitalis.
Pulse rate 78 to the minute.

between "v" and "c" in this figure. Fig. 11,D is from the same case after restoration of the normal mechanism following digitalis. This case was confirmed by the electrocardiograph.

AURICULAR FIBRILLATION.

In auricular fibrillation the jugular curve is characterized by (a) the absence of all "a" waves; (b) the conspicuous summits of the jugular tracing fall during the sphygmic period, and (c) the occasional occurrence of "f" waves. The radial curve is characterized by (a) no evidence of a dominant rhythm; (b) the length of the individual radial beats varies from one cardiac cycle to the next; (c) the irregularity does not repeat itself; (d) the long pauses are not simple multiples of the shortest pause, and (e) the height of the radial wave frequently bears no relation to the length of the preceding pause. The pulse is said to be totally irregular.

The jugular curve constitutes the so-called ventricular form of venous pulse. Fig. 13,A and B illustrate typical examples of the tracings seen in this condi-

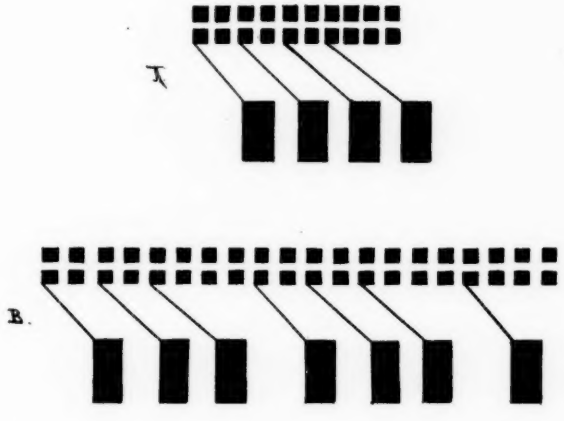


Fig. 12.—A. Diagram illustrating a 2:1 ratio in auricular flutter.
B. Diagram illustrating alternating ratios of ventricular response in auricular flutter.

tion; the latter figure showing the plateau type of ventricular venous pulse. The analysis is self-evident.

PULSUS ALTERNANS.

A true alternating pulse is one in which there is present a normal rhythm, the radial spaces accurately but the radial waves vary in height from one cardiac cycle to the next. It is regarded as of grave clinical significance.

RULE FOR CALCULATING THE PULSE RATE.

To calculate the cardiac rate from a given tracing, space off thirty 1-5ths on the time marker tracing; transfer this measurement to the radial curve placing the left hand end at the up-stroke of any radial wave. Beginning with this radial, as 1, count the number of beats, and fraction of a single beat, included within this measurement and multiply the number found by 10.

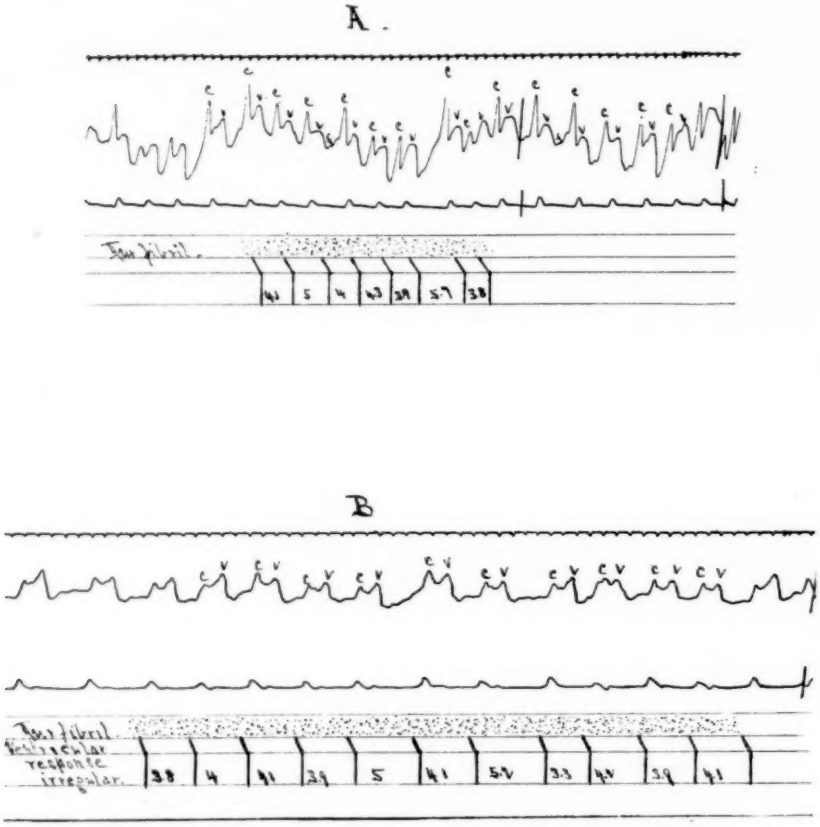


Fig. 13.—A. Auricular fibrillation. Note the absence of all "a" waves from the jugular tracing, the total irregularity of the radial curve and also that "c" and "v" fall during the sphygmic period.
B. Auricular fibrillation. Plateau type of venous pulse.

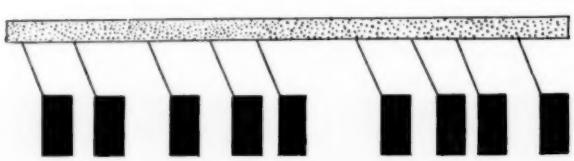


Fig. 14.—Diagram illustrating the nature of the disturbance in auricular fibrillation. Upper dotted space represents the auricles in the state of fibrillation. The ventricle responds at varying intervals to the haphazard impulses coming from the auricle.

CONCLUSION.

The fundamental principles of the polygraphic tracings and the method of procedure in their analysis have been described, as simply as possible. Their value as an aid to the proper understanding of many cardiac conditions has been emphasized, and their importance in the correct diagnosis of the cardiac arrhythmias insisted upon.

BIBLIOGRAPHY.

[1]Mackenzie, James: The Study of the Pulse, Arterial Venous and Hepatic and of the Movements of the Heart, Edinburgh and London, 1902.
Diseases of the Heart, 3rd Edition; Oxford University Press, Henry Frowde, London, 1913.
[2]Lewis, Thomas: The Mechanism of the Heart Beat, Shaw & Sons, London, 1911.
[3]Gibson, A. G.: On a Hitherto Undescribed Wave in the Venous Pulse, Lancet, London, 1907, ii, 1380.
[4]Hirschfelder, A. D.: Some Variations in the Form of the Venous Pulse, Bull. Johns Hopkins Hosp., 1907, xviii, 265.
Diseases of the Heart and Aorta, J. B. Lippincott Co., Phila., 1910, 55.
[5]Lewis, Thomas: Clinical Disorders of the Heart Beat, Shaw & Sons, London.
Ritchie, W. T.: Auricular Flutter, W. Green & Son, Edinburgh and London, 1914.
Wenkebach, K. F.: Arrhythmia of the Heart—A Physiological and Clinical Study; English translation by Thomas Snowball, W. Green & Sons, Edinburgh and London, 1904.

THE DIAZO AND UROCHROMOGEN REACTIONS AS PROGNOSTIC AIDS IN PULMONARY TUBERCULOSIS*

By H. J. Corper, M.D., and F. F. Callahan, M.D., Chicago, Ill.

IN the hope of verifying or disproving the general conception regarding the prognostic value of the urochromogen reaction, and of comparing the value of Ehrlich's Diazo and Weisz' urochromogen tests, it was thought desirable to study these reactions in the urines of a large series of carefully observed tuberculous patients. The diversity of opinions reached from results obtained by a large number of observers also made this investigation desirable.

In reviewing the literature it seems hardly necessary to consider the diazo reaction of Ehrlich, since its value as a prognostic aid is so well established. The urochromogen reaction developed from a study made by Weisz[1] covering a period of about five or six years, which led him to the conclusion that there are two urochromogens or precursors of the yellow urinary pigment, one of these urochromogen α which can be oxidized by potassium permanganate, potassium persulphate, etc., into urochrom, the other, urochromogen β, which gives the diazo reaction of Ehrlich.

Schnitzker[2] who studied these substances from a chemical standpoint was able to separate and differentiate, although not quantitatively urochromogen α and β; showing definitely that they were distinct chemical substances. Weisz[3] in a further contribution states that the presence of urochromogen in the urine precedes the diazo reaction and answers all its purposes. He gives the ultimate history of twenty-three patients tested in this way, confirming the great prognostic value of this test. The earliest American observations on the urochromogen test, as far as we could find, were made by Heflebower[4] who studied 39 cases of pulmonary tuberculosis and concludes that the urochromogen test is a better index as to prognosis than the diazo reaction; also that the intensity of these reactions is the important factor in the prognosis. Paranhos and Giolito[5] studied the reaction in 50 healthy patients who always gave negative tests and 50 tuberculous patients which were all positive but 5; three of the latter being very far advanced. The reaction was not dependent upon the severity of the disease. In 50 cases suffering from other diseases (syphilis, nephritis, etc.) a positive reaction was obtained in 24. Vitri[6] studied 150 cases of tuberculosis and found the reaction slight or absent in extrapulmonary lesions, also absent in incipient pulmonary cases running a chronic course. He also found the diazo reaction to be less sensitive than the urochromogen test. He concluded that a negative skin tuberculin reaction with a positive urochromogen indicates extension of the tuberculosis. Tuliato[7] found the urochromogen test positive in 67 per cent of all fatal cases in various diseases; it is not specific for any one disease; but is a sign of the gravity of the condition and explains it as due to oxidation of albuminoid substances originating in the decomposition of cells as the result of direct or indirect action of pathogenic organisms.

*From the Laboratories of the Municipal Tuberculosis Sanitarium of the City of Chicago.

Weisz[8] in a later article states that the appearance of urochromogen in the urine indicates that a local circumscribed tuberculous process has become generalized. The urochromogen disappears when the organism gets the upper hand, and the longer the reaction has existed the graver the prognosis. Cummings[9] as a result of the examination of 100 cases concludes that the urochromogen and diazo reactions appear in the urine of a majority of the patients in a late stage of pulmonary tuberculosis. These reactions do not appear, however, until long after a correct unfavorable prognosis is possible by careful clinical examinations. Gullbring[10] obtained only 2 cases out of 168 (mostly advanced stage of tuberculosis) in which the diazo reaction was positive and urochromogen negative, in 114 of these the findings were parallel, they were both negative in 88 and positive in 26. In all the others (37 per cent) the urochromogen was positive with negative diazo and these showed, besides the pulmonary lesions signs of amyloid disease. The urochromogen test was positive in 90 per cent of the amyloid cases while the diazo in only 20 per cent.

Metzger and Watson[11] examined 113 cases of tuberculosis with the urochromogen test and obtained negative results in 5 incipient cases, 32 per cent positive in 28 moderately advanced cases and 55 per cent positive in 80 far advanced cases, and conclude that the presence of the urochromogen reaction in the urine is of unfavorable prognostic import for the time being. Its persistent presence in spite of proper treatment probably means a hopeless prognosis. Its absence is generally, although not invariably, of good prognostic import regardless of clinical appearances. A prompt and continued disappearance is a favorable sign. Burgess[12] in a recent publication reports 469 urochromogen tests in 171 tuberculous patients and 1,030 tests on 650 non-tuberculous patients (suffering from other diseases) with but 26 positive tests in the latter which proved to be of no clinical significance. Fifty-five of the 171 tuberculous patients gave a positive test, and 30 of these died within three months, 6 within 6 months and 1 within 1 year; the remainder were either worse, or observations discontinued. He concludes that the urochromogen test is of no value in determining the prognosis in non-tuberculous diseases; a positive reaction in advanced tuberculosis indicates progress of the disease with probable termination in 3 to 6 months, while a negative test is of no value. Shortly following there appeared a paper by Sinclair[13] on the diazo and urochromogen tests in 146 cases of pulmonary tuberculosis. Both tests were negative in 38 cases of which 71 per cent improved, 18.4 per cent progressed and 10.6 per cent died. Both tests were positive in 7 cases, all of which died. In 23 cases the diazo reaction was positive with negative urochromogen and 25.7 per cent of these improved, 26.1 per cent progressed and 48.2 per cent died. In 78 cases the diazo was negative with positive urochromogen, 79.5 per cent of these improved, 15.4 per cent progressed and 5.1 per cent died. He concludes that a change from both negative to a negative diazo and positive urochromogen is more favorable than to a positive diazo and negative urochromogen. Both positives generally indicate an early death. A change from a positive diazo and negative urochromogen is favorable only on reversal (that is, to a negative diazo and positive urochromogen). If the urochromogen does not appear concomitantly with the disappearance of the diazo the prognosis is bad.

In order to observe whether there is any relation or difference between the occurrence of the diazo and urochromogen reactions in the various stages of pulmonary tuberculosis, the cases (350 in all) were studied after dividing them according to the National Association classification into incipient, moderately advanced and far advanced. To show further whether there was any relation between these reactions and the progress of the disease the examinations were classified depending upon whether the cases improved or not, giving two divisions as improved and unimproved. Since the study was to cover not only the prognostic value of both reactions but also the relation between the reactions and the value of each and both, it was necessary to note when the reactions were both present, individually present, or absent, and the changes that occurred on subsequent examinations. With these things in mind the cases were finally tabulated into the form shown in Table I.

As a result of the classification of the cases and reactions as shown in Table I it is to be noted that of the 82 incipient cases on whom 197 examinations were made, not one diazo reaction, whereas 8 positive urochromogens were obtained on initial examination; 4 of these 8 (2 of which were single examinations) improved and became negative, while 2 were unimproved and became

TABLE I.—CHANGE OF REACTION ON ADMISSION AND SUBSEQUENTLY. CLASSIFIED.

			D+U+	D+U−	D−U+	D−U−
Incipient cases, total exams. 197 on 82 patients	Initial Examination.				8 2-single exams.	74 25-single exams.
	Subsequent Examinations, Improved.	D+U+				
		D+U−				
		D−U+				4
		D−U−			4	
	Subsequent Examinations, Unimproved.	D+U+				
		D+U−				
		D−U+				1
		D−U−			2	44
Moderately advanced cases, total exams. 256 on 112 cases.	Initial Examination.		4 4-single exams.	1 1-single exam.	12 6-single exams.	95 35-single exams.
	Subsequent Examinations, Improved	D+U+				
		D+U−				2 1-with pleural effusion
		D−U+				3
		D−U−			6	35
	Subsequent Examinations, Unimproved.	D+U+				
		D+U−				2 1-with pleural effusion
		D−U+				3
		D−U−				15
Far advanced cases, total exams. 502 on 156 cases.	Initial Examination.		25 9-single exams.	5 2-single exams.	13 2-single exams.	113 21-single exams.
	Subsequent Examinations, Improved	D+U+				2 1-with erysipelas
		D+U−	1			
		D−U+				2
		D−U−	6		5	22
	Subsequent Examinations, Unimproved.	D+U+	5		1	10
		D+U−	1	1	1	
		D−U+			1	3
		D−U−	3	2	3	53

negative. The remaining 74 gave negative reactions for both tests on initial examination, 18 of these improved, of which 14 had only initial examinations and 4 gave positive urochromogen tests on subsequent examinations; 56 were unimproved (11 of these were only single examinations), one of the remaining 45 gave a positive urochromogen on subsequent examination and 44 remained negative.

Of 112 moderately advanced cases with a total of 256 examinations 4 revealed both urochromogen and diazo positive, and one case gave a positive urochromogen and negative diazo (no subsequent examinations being made on these 5 cases). Twelve cases gave a negative diazo and positive urochromogen, 6 of which were only initial examinations, and 6 cases improved and became negative on all subsequent examinations. Ninety-five cases were negative to both reactions, 35 of these having only initial examinations; 40 cases improved of which 2 gave a positive diazo and negative urochromogen (one having had a pleural effusion), 3 revealed a negative diazo and positive urochromogen, and 35 remained negative throughout. Twenty of the 95 diazo negative urochromogen negative initial cases were unimproved, 2 giving a positive diazo and negative urochromogen (one of these had a pleural effusion), 3 cases a negative diazo and positive urochromogen, and 15 remained negative throughout.

Of 156 far advanced cases upon which a total of 502 examinations were made, 25 gave both reactions positive upon the first examination, 7 of these 25 improved (9 only had initial examinations) one of which became positive diazo and negative urochromogen and the remaining 6 became negative. There were 9 unimproved cases; 5 remained positive diazo and positive urochromogen, one became positive diazo and negative urochromogen, and 3 became negative to both reactions on subsequent examinations. Five cases gave positive diazo and negative urochromogen on admission, of which 2 were only initial examinations, and the remaining 3 were unimproved—1 of these remained positive diazo and negative urochromogen while the other 2 became negative to both tests. Of 13 cases which gave negative diazo and positive urochromogen on admission, 2 were initial examinations only, 5 improved and became negative to both tests and 6 were unimproved of which 1 became positive to both tests, one positive diazo and negative urochromogen, 1 remained the same and 3 became negative to both tests. Both reactions were negative on initial examination in 113 cases (21 of these being only single examinations), 26 improved—2 of which became positive to both tests (one of these during an attack of erysipelas), 2 became negative diazo and positive urochromogen and 22 remained negative on subsequent examinations. Of the 113 cases 66 were unimproved, 10 of which became positive to both tests, 3 became negative diazo and positive urochromogen and 53 remained unchanged on subsequent examinations.

The large number of negative reactions in the far advanced cases and an endeavor to explain these reactions made it seem advisable to further classify 103 far advanced cases into cases with far advanced physical signs and few symptoms, as far advanced fibroids, and those showing far advanced signs and active symptoms as far advanced active cases. The result of this classification is shown in Table II.

TABLE II.—COMPARISON OF REACTIONS IN FAR ADVANCED FIBROID AND FAR ADVANCED ACTIVE CASES.

			D+U+	D+U—	D—U+	D—U—
Far advanced Fibroid cases.	Initial Examination.		5 1-single exam. 3-acute exacerbations 1-spontanous pneumothorax on admission	2	4	63 5-single exams.
	Subsequent Examinations.	D+U+				3 including 1-enteritis 2-acute exacerbations
		D+U—				
		D—U+			1	4
		D—U—	4	2	3	51
Far advanced Active cases.	Initial Examination.		7 4-single exams.	1	2	19 3-single exams.
	Subsequent Examinations.	D+U+	2		2	10
		D+U—	1			1
		D—U+				
		D—U—		1		5

In this table there were classified 74 far advanced fibroid and 29 far advanced active cases. Of the fibroid cases 5 were positive diazo and positive urochromogen on admission (one only having an initial examination) 3 of these 5 had acute exacerbations and 1 had acute pneumothorax when examinations were made; 4 became negative on subsequent examinations. Of the 74 fibroid cases 2 had positive diazo and negative urochromogen on admission and became negative to both tests; 4 had negative diazo and positive urochromogen on admission of which 1 remained the same and the other 3 became negative to both tests on subsequent examinations. There were 63 of the far advanced fibroid cases which gave negative to both tests on initial examination (5 of these being single examinations), 3 cases (1 developing tuberculous enteritis and 2 during an acute exacerbation) became positive diazo and positive urochromogen. Four changed to negative diazo and positive urochromogen and 51 remained unchanged on subsequent examinations.

Of the 29 far advanced active cases 7 were positive to both tests on admission (4 of these were single examinations), 2 remained the same on subsequent examinations and 1 became positive diazo and negative urochromogen. Only 1 of the 29 cases gave a positive diazo and negative urochromogen reaction on admission and subsequently became negative to both tests. Two cases were negative diazo and positive urochromogen on initial examination and became positive to both reactions subsequently. Nineteen cases gave a negative reaction to both tests on admission (3 of these being only initial examinations), 10 became positive diazo and positive urochromogen, 1 became positive diazo and negative urochromogen and 5 remained unchanged on subsequent examinations.

The terminal cases, of which there were 60, were tabulated separately in Table III.

TABLE III.—CLASSIFICATION OF REACTIONS IN TERMINAL CASES.

Initial Examination		D+U+ 34 15-single exams.	D+U— 6 3-single exams.	D—U+ 5 4-single exams. 1-terminal hemorrhage	D—U— 15 3-single exams. 1-terminal hemorrhage
Subsequent Examinations 133 examinations. on 60 cases.	D+U+	14	2		4
	D+U—	2			
	D—U+	2 including 1-T. B. meningitis		1	3 including 1-terminal hemorrhage 1-acute peritonitis
	D—U—	1 including 1-T. B. meningitis	1		5 including 2-T.B. meningitis 1-terminal hemorrhage 1-acute lobar pneumonia 1-acute cardiac

Of these 60 terminal cases 34 gave a positive diazo and urochromogen reaction on initial examination (15 of these being only single examinations), 14 remained positive on subsequent examination, 2 changed to positive diazo and negative urochromogen and 2 changed to negative diazo and positive urochromogen, while 1 became negative. One of the 2 cases that changed to negative diazo and positive urochromogen died of tuberculous meningitis.

Six of the 60 cases were positive diazo and negative urochromogen on initial examination (3 of these were single examinations), 2 changed to positive diazo and urochromogen and one to negative diazo and negative urochromogen on subsequent examinations.

Five of the terminal cases gave a negative diazo and positive urochromogen on initial examination (4 being single examinations, one of which died of terminal hemorrhage), one showed no change subsequently. Fifteen of the terminal cases gave negative results on initial examination (3 of which were single examinations, one of these dying of terminal hemorrhage), 4 became positive to both reactions on subsequent examinations; 3 became negative diazo and positive urochromogen including one who died of terminal hemorrhage, and one from acute peritonitis due to a perforation of a tuberculous ulcer, and 5 remained negative [2 of which died from tuberculous meningitis, 1 from a terminal hemorrhage, 1 of acute lobar (pneumococcus) pneumonia, and one from cardiac insufficiency].

It is to be noted from these tabulated results of the findings in terminal cases that practically all cases dying of pulmonary tuberculosis reveal positive reactions by both tests at some time during the last 6 months of their disease. Those cases which gave negative reactions to both tests during the last 6 months of the disease usually died of some acute condition such as pulmonary hemorrhage or tuberculous meningitis, etc. It was noted that cases dying of tuber-

culous meningitis usually gave negative reactions to both tests; this was especially true of the diazo reaction. Some of these cases were negative during the whole course of the disease, others became negative during the attack of meningitis.*

CONCLUSIONS.

1. Cases dying of pulmonary tuberculosis give a positive diazo and urochromogen test at some time during the last 6 months of their illness. Whenever both tests are negative during this period death was found to be due to some intervening condition, such as pulmonary hemorrhage, tuberculous meningitis, etc.

2. Cases of chronic fibroid tuberculosis generally give both reactions negative except when same is explicable by some acute exacerbation, acute intercurrent infection or acute pleural effusion.

3. In active cases of pulmonary tuberculosis when both reactions are positive and remain so for most of the succeeding examinations it is of grave prognostic import. When both reactions are negative in acute cases no stress can be laid upon the findings.

4. There seems to be no regularity between the presence of either reaction, its disappearance to be displaced by the other or by both.

5. The presence of a urochromogen reaction in cases showing no clinical symptoms is of no prognostic value. No diazo reactions were obtained in clinically inactive cases, whereas a number of urochromogen reactions were obtained in such cases.

6. The presence of a diazo or of both reactions is a *danger signal* of grave import.

7. Careful clinical observations will, from a prognostic standpoint, give more information than the diazo and urochromogen tests in pulmonary tuberculosis.

8. Wherever possible both tests should be performed, but of the two the diazo should be given the preference.

*We wish to express our appreciation to Dr. M. I. Marshak for the kind assistance rendered in preparing this paper.

THE HOSPITAL CHEMICAL LABORATORY*

By N. W. Janney, M.D., Ph.D., New York City.

PRESENT STAGE OF DEVELOPMENT OF THE HOSPITAL LABORATORY.

THE development of the American hospital laboratory seems curiously enough to have lagged far behind the modern evolution of the medical sciences. The "laboratory" of even the large urban hospital of not so many years ago still very frequently presented little evidence of advance. A young physician often in active practice was frequently found in sole charge of the laboratory work,—bacteriological, chemical, pathological, and serological. His assistants were as a rule resident physicians who, bent on a purely clinical career, found the clinical side of medicine so engrossing that their laboratory duties frequently suffered as a consequence. Under these circumstances it is then not surprising that the newer delicate scientific methods of precision were inadequately carried out and that but relatively little original research of value resulted from such an organization. So the physical equipment of such a laboratory was as a rule but illy provided for or indeed neglected. This materially contributed to a generally unsatisfactory state of affairs.

In order to meet such needs many of the larger city hospitals, the institutions directly connected with universities being excepted throughout this discussion, have developed so-called "laboratories of clinical pathology" which represent about the present stage of evolution of the hospital laboratory. The head of such a laboratory who now more frequently devotes his entire time to his hospital duties, is usually a pathologist or bacteriologist and often intends following a wholly scientific career. This implantation of a purely scientific man into the hospital system represents a decided step in advance. Numerous examples can be quoted where research studies of important nature have been carried out under these circumstances. The "clinical pathologist" has become so generally recognized that in certain universities chairs of clinical pathology have been created. There is indeed no doubt that the research as well as routine in pathology, bacteriology and serology done in many large hospitals can now be said to be entirely on a par with the modern development of these scientific medical branches.

NEED OF A HOSPITAL BIOCHEMICAL LABORATORY.

At the present time we are however in the midst of a great era of expansion of chemical knowledge as applied to medicine. It can only be likened to the previously occurring rapid development of bacteriology when its possibilities became clearly recognized. Within the past two decades the pure chemists, headed by Emil Fischer, have made such advances in the field of physiological chemistry, animal and human, that the combined work of all previous time has been surpassed. No other example than protein chemistry need be considered in order to emphasize the truth of this assertion.

Some time back the physician trained in clinical pathology could with no

*From the Chemical Laboratory of the Montefiore Home and Hospital for Chronic Invalids, New York City.

great effort include among his duties the chief chemical examinations then deemed advisable to be carried out in the hospital laboratory. Such procedures as compared to the total work of the laboratory were few and usually required no unusual technical skill of chemical nature. This state of affairs has, however, changed considerably of late. Newly introduced biochemical methods are becoming ever increasingly such direct aids to clinical diagnosis and treatment that of the total clinical laboratory examinations a large percentage are already chemical. The newer methods for the quantitative determination of various constituents of the blood may here be mentioned as an example. In many instances a greater knowledge of chemistry and technic is also required in order to obtain accurate analytical results by these new methods than can be fairly expected of the physician with his necessarily general training, without undue loss of time and energy.

The prevailing type of hospital laboratory, as alluded to above, certainly seems but poorly prepared to cope with these new demands made on it by biochemistry. In organization essentially medical from director down, there is frequently no one connected with it on whom chemical examinations of a complex nature can properly devolve. This fact was very forcibly impressed on the writer in a comparative study recently made by him of hospital laboratories. Frequently first rank institutions were found to possess experienced pathologists, serologists and bacteriologists quite competent to fill higher university positions, whereas it is a matter of great rarity that the biochemist, when such a post is actually existent, possesses such qualifications. Indeed only a very few existing instances are known of hospital chemical laboratories developed commensurately with the position now attained by biochemistry among the medical sciences.

IMPORTANCE OF THE HOSPITAL CHEMICAL LABORATORY FOR BIOCHEMICAL RESEARCH AND TEACHING.

In considering the relations of chemistry and medicine of today a certain lack of perspective is often observable in the work of both chemists and physicians engaged in the physiological chemical field. As extreme examples the following two episodes may be quoted. A certain large city hospital in Germany, deciding on modernization, secured the services of an organic chemist who was instructed to enter into research studies of clinical importance. This worker knowing that hemoglobin is an important blood constituent spent two years and would have probably spent many more if he had been permitted, in working on *the configuration of the hemoglobin molecule*. The vague relation of this research to clinical medicine is quite obvious.

The second incident is of the opposite nature. A young physician secured a position to do research work in biochemistry. With the intensest devotion and application he succeeded after a year in introducing a single quite unimportant modification into a standard biochemical analytical method. This work, however creditable to its author in view of his limited chemical training, can hardly be said to represent an adequate return of the time and money involved. But such illustrations of inexperience are at least useful in emphasizing a criticism which may be made of present day biochemical research and teaching. Too often an unfortunate one-sidedness is apparent in the biochemical research

worker or teacher. This tendency to uneven development may be either in the chemical or medical direction, but usually the chemical is the predominating. As a result the purely chemical side of this truly border subject is often rather over dwelt upon. Indeed the research studies of certain university departments of physiological chemistry would do like honor to a university chemical institute. Owing to the same one-sidedness, medical students are not always sufficiently drilled in those portions of biochemistry most useful to their careers as practitioners.

The underlying cause of these difficulties lies in the fact that it is not easy to acquire the ideal blending of chemical and medical experience most desirable for research workers and teachers of biochemistry. The pure chemist has far too few opportunities in the university department of physiological chemistry to come into needed contact with the clinical side of medicine. Conversely if beginning his biochemical career as a physician and receiving his introduction to biochemistry in a hospital laboratory, the fundamental chemical training of this future investigator and teacher of biochemistry often remains permanently inadequate.

If, however, our large hospitals possessed efficient chemical laboratories conducted by biochemists of broad experience, they could serve as nearly ideal training places for future workers in this field. Here the young chemist could come into daily contact with medical internes as well as patients, learn something of morbid conditions at first hand, and in general enjoy a peculiarly rich opportunity for acquiring much of the medical knowledge necessary for his future development as a biochemist. After some years spent in this atmosphere he could then accept a position in a university department of biochemistry with every prospect of keeping a proper balance between the chemical and medical side of his subject.

Another reason may here be mentioned for the need of development of hospital biochemical laboratories. It is in the hospital and not so frequently in the university departmental biochemical laboratory as at present that the biochemist should also find material for original investigation. The writer in delving through medical literature has many times been impressed by the advances which could have been made had many questions been studied by biochemists rather than been left to their purely medical confreres, whose enthusiasm for objects of chemical research frequently far surpasses their chemical attainments. If the biochemist had been at hand in the hospital many of such investigations would have had higher value.

RELATION OF THE CLINICAL STAFF TO THE HOSPITAL BIOCHEMIST.

A very unfortunate arrangement is frequently met with in hospitals at present. Owing to shortness of funds or to a lack of realization of the value of an experienced biochemist to the institution, a young worker in this field is frequently placed in charge of the chemical laboratory. Such an incumbent very frequently fails of proper development, this being due to his premature isolation and separation from older biochemical colleagues. Another patent cause for the lack of success of hospital laboratories may also play a role, namely a too great control of the work, especially of research, on the part of the clinical authorities. This may be necessary in the case of the

young and inexperienced chemist who might otherwise fail to devote himself to well judged research problems. However in many otherwise well organized hospitals the belief seems still to persist that the control of the research activities of the chemist and indeed also of all branches of hospital laboratory research should lie with the clinical staff. It is very surprising that such an obviously detrimental arrangement should, in view of the modern development of medicine, require much discussion. Objectively considered it seems no more reasonable that the experienced original investigator in the scientific medical branches should have his problems selected for him by the clinician, than it would be for him to attempt to prescribe changes in the treatment of the hospital patients under control of the visiting physicians. It is, however, as fully recognized by the writer with regard to his own subject that only to one of broad training both in medicine and chemistry can such independence be safely given in choice of hospital laboratory problems. In this lies an additional argument for furthering the development of a type of original investigator in biochemistry having the hospital training suggested in this article.

What then constitutes the most judicious relation of the visiting physician to the hospital biochemist? Prof. Frederick Müller of Münich once expressed to the writer the conviction that the *"Fragestellung"* should be the aim of the clinician with regard to biochemical research. The discerning bedside physician coming into intimate contact with the innumerable variations of morbid phenomena has indeed many occasions to formulate questions often of extreme interest and importance to the biochemist. It remains for the latter, however, to judge of the feasibility of a chemical attack on such questions and to devise means for the solution of such as lend themselves to elucidation. Again many other problems can best be studied by the clinician, biochemist, and at times also the pathologist working in common. Many valuable researches of recent years have been made possible only by such an efficient coalition of specialized knowledge and experience.

ORGANIZATION OF A HOSPITAL BIOCHEMICAL LABORATORY.

Providing that an adequately trained and experienced biochemist is obtainable this should present no great difficulty. As previously discussed it is at present quite rare to find men sufficiently versed in both medicine and chemistry to become ideal incumbents of such positions. To its holder are frequently referred problems involving very considerable knowledge of clinical medicine. On the other hand the solution of many questions may tax all the resourcefulness of an able chemist. The work of the director of such a laboratory can be best carried on with the help of an assistant chemist, who also receives medical experience as suggested above. If funds permitted, other assistants could be employed for research problems only. One or more technicians for the simpler chemical routine such as urinalysis and gastro-analysis could complete the staff.

In hospitals affiliated with universities the director of the hospital chemical laboratory could likewise hold an assistant or associate professorship in the teaching institution. Certain biochemical students preparing themselves for their doctor's degree could then be given an opportunity for the working out of their theses in the laboratory. In this way, also, it is possible to more evenly blend medical with chemical experience in the development of the future biochemist.

As to the physical equipment, four categories should be considered. (1) the chemical laboratory, (2) the metabolic ward, (3) provision for animal experimentation, (4) library. For the hospital chemical laboratory to meet the requirements suggested in this article very judicious equipment is necessary. The routine chemical analyses of urine, blood, gastric fluid, etc., can best be carried out in a separate room. Other space should if possible be reserved for purely research studies. This division is but rarely seen as yet, but is of considerable importance to the workers. As the problems and therefore the chemical operations carried out in this laboratory vary constantly, it is very important to install only such apparatus as permits of being easily changed about to meet the shifting requirements of the work. In an article of this kind it seems inadvisable to go into details of this and a number of other very practical matters of similar nature.

As a matter of common experience, it is very difficult to properly carry out metabolic examinations and experiments in the midst of an active medical ward. Segregation of patients undergoing such studies as well as their complete control is essential for the proper conduct of such work. For most requirements two small rooms for male and female patients with a conveniently situated special diet kitchen are adequate. Too much care can scarcely be given to the training of the dietician and nursing staff of such an experimental ward, inasmuch as the entire value of a long and laborious metabolic study is directly dependent on the faithfulness and accuracy of the dieting of the patient and collection of the excreta. The location of this ward should if possible be directly adjacent to the chemical laboratory.

As the animal rooms available to the biochemist in a hospital are scarcely ever set aside exclusively for his use, their equipment must depend somewhat on the needs of the other scientific workers. In general the plan adopted by the Stadt Krankenhaus at Frankfurt am Main, Germany, seems a good one and may be mentioned. Rooms for dogs and smaller animals, a room for experimental procedures, such as catheterization requiring at most simple sterile precautions, together with a well furnished aseptic animal operating room and anteroom enter into the makeup of this plant.

Provision for a working library even if necessarily very restricted in size should be made in such a complete laboratory development. Very few hospital libraries in America known to the writer are in any way adequate to the calls made upon them by the various workers. The reason often given in explanation of such a deficit in ready-to-hand knowledge is that such books are too expensive to acquire. As a matter of fact one thousand dollars judiciously invested by a competent authority suffices to obtain a very useful working set of journals and text-books in any one of the scientific medical branches. When it is considered that the mechanical equipment of the American laboratory is often more than adequate for its purposes and unnecessarily expensive as well, it would be wiser, the writer believes, to devote to library purposes some of the money often represented by little used pieces of large apparatus and such luxuries as plate glass shelves.

Inasmuch as the general arrangement of the laboratories of the new Montefiore Home and Hospital has been demonstrated through several years of use

to be convenient, mention may be made of their general plan. One of the buildings belonging to the hospital complex is occupied by male and female medical wards on its first two floors. The third floor of this building is occupied by the laboratories adjacent to which is a small experimental ward, diet kitchen and the research library. Immediately over the laboratory floor are built the animal rooms. This close physical association of the various elements going to make up the laboratories has proven of considerable advantage.

THE NINHYDRIN COLOR REACTIONS OF PROTEINS AND THEIR SPLIT PRODUCTS*

By Herbert W. Emerson, M.D., and John S. Chambers, M.S.,
Ann Arbor, Mich.

THE NINHYDRIN REACTION.

THE ninhydrin color reaction[2, 3] was first tried on the poison cleaved from casein. The poison was made up in aqueous solutions (1-100); (1-1,000) and (1-10,000). The acidity was determined and neutralized with N/10 sodium hydroxide. The color test was performed by taking 1 c.c. of this solution in a small, narrow test tube and adding one drop of a one per cent ninhydrin solution and placing it in a rack in an oil bath kept at 120° C., and leaving it there for two minutes; then the tube was removed and permitted to cool. The solution (1-100) gave a light reddish-violet color; the solution (1-1,000) gave no color to the liquid but deposited a blue line upon the sides of the test tube at the surface of the solution. The solution (1-10,000) was negative, no color and no ring. This experiment was controlled by glycocoll solutions of similar strengths. Glycocoll solutions (1-100) and (1-1,000) gave a deep blue color and the solution (1-10,000) gave a very pale blue color which deepened some upon standing for one hour and then gradually faded.

We tested in the same way poisons cleaved from colon bacilli; from the bacilli of tuberculosis; from dog's muscle; from dog's liver; and from beef's kidney; and the results were as they are described in the casein poison with slight variations in intensity of color.

The next series of experiments were performed in order to determine whether anything in the protein poison solution interfered with the ninhydrin reaction.

Experiment I was performed with casein poison solution (1-100) and adding glycocoll (1-100) and ninhydrin and heating as before.

Table I.

Casein poison (1-100).	Glycocoll (1-100).	1% ninhydrin.	Results.
1 c.c. casein solution	+ 1 drop glycocoll	+ 1 drop ninhydrin and heat	—
1 c.c. " "	+ 2 drops "	+ 1 " " " "	—
1 c.c. " "	+ 4 " "	+ 1 " " " "	—
1 c.c. " "	+ 8 " "	+ 1 " " " "	Weak +
1 c.c. " "	+ 16 " "	+ 1 " " " "	Fair +
1 c.c. " "	+ 32 " "	+ 1 " " " "	Good +

*From the Hygienic Laboratory of the University of Michigan.
This investigation was suggested and part of the work directed by Dr. V. C. Vaughan.
These experiments were performed on poisons cleaved from various proteins according to Vaughan's method.[1]

This experiment was repeated but the casein poison solution was first neutralized.

TABLE II.

CASEIN POISON (1-100).	GLYCOCOLL (1-100).	1% NINHYDRIN.	RESULTS.
1 c.c. casein solution	+ 1 drop glycocoll	+ 1 drop ninhydrin and heat	—
1 c.c. " "	+ 2 drops "	+ 1 " " " "	Weak +
1 c.c. " "	+ 4 " "	+ 1 " " " "	Fair +
1 c.c. " "	+ 8 " "	+ 1 " " " "	Good +

The above experiment was repeated using casein poison solution (1-1,000).

TABLE III.

CASEIN POISON (1-1000).	GLYCOCOLL (1-100).	1% NINHYDRIN.	RESULTS.
1 c.c. casein solution	+ 1 drop glycocoll	+ 1 drop ninhydrin and heat	Weak +
1 c.c. " "	+ 2 drops "	+ 1 " " " "	Fair +
1 c.c. " "	+ 4 " "	+ 1 " " " "	Good +

The above experiment was repeated using a casein poison solution (1-10,000).

TABLE IV.

CASEIN POISON (1-10,000).	GLYCOCOLL (1-100).	1% NINHYDRIN.	RESULTS.
1 c.c. casein solution	+ 1 drop glycocoll	+ 1 drop ninhydrin and heat	+
1 c.c. " "	+ 2 drops "	+ 1 " " " "	Good +

These experiments indicate that there is something in the casein poison solution which lessens the delicacy of the ninhydrin reaction. Comparison of tables I and II shows that the slight acidity of the casein poison solution is in this respect an important factor, but comparison of tables III and IV indicates that there are other factors and that the diluting of the casein poison solution markedly lessens this inhibitory action so that it is not appreciable in dilutions of 1-10,000.

Some experiments to determine the effect of dilute hydrochloric acid on the ninhydrin reaction.

Experiment I, using Glycocoll (1-1,000) and n/10 HCl.

TABLE V.

GLYCOCOLL (1-1,000).	N/10 HCl.	1% NINHYDRIN.	RESULTS.
1 c.c. glycocoll		+ 1 drop ninhydrin and heat	+ + + + +*
1 c.c. "	+ 1 drop n/10 Hcl	+ 1 " " " "	—
1 c.c. "	+ 2 drops " "	+ 1 " " " "	—

Experiment II, using n/50 HCl.

TABLE VI.

GLYCOCOLL (1-1,000).	N/50 HCl.	1% NINHYDRIN.	RESULTS.
1 c.c. glycocoll	—	+ 1 drop ninhydrin and heat	+ + + + +*
1 c.c. "	+ 1 drop n/50 Hcl	+ 1 " " " "	+ + +
1 c.c. "	+ 2 drops " "	+ 1 " " " "	+
1 c.c. "	+ 3 " " "	+ 1 " " " "	—
1 c.c. "	+ 4 " " "	+ 1 " " " "	—

Experiment III, using n/100 HCl.

TABLE VII.

GLYCOCOLL (1-1,000).	N/100 HCl.	1% NINHYDRIN.	RESULTS.
1 c.c. glycocoll	—	+ 1 drop ninhydrin and heat	+++++
1 c.c. "	+ 1 drop n/100 Hcl	+ 1 " " " "	++++
1 c.c. "	+ 2 drops " "	+ 1 " " " "	+++
1 c.c. "	+ 3 " " "	+ 1 " " " "	++
1 c.c. "	+ 4 " " "	+ 1 " " " "	+
1 c.c. "	+ 5 " " "	+ 1 " " " "	—

Small quantities of dilute inorganic acids interfere with and prevent the ninhydrin color reactions.

Experiment IV, using n/10 Oxalic acid.

TABLE VIII.

GLYCOCOLL (1-1,000).	N/10 OXALIC.	1% NINHYDRIN.	RESULTS.
1 c.c. glycocoll	—	+ 1 drop ninhydrin and heat	+++++
1 c.c. "	+ 1 drop n/10 oxalic	+ 1 " " " "	+
1 c.c. "	+ 2 drops " "	+ 1 " " " "	—

*++++ + indicates a deep blue color.
+ indicates a pale blue or violet color.

Experiment V, using n/50 Oxalic acid.

TABLE IX.

GLYCOCOLL (1-1,000).	N/50 OXALIC ACID.	1% NINHYDRIN.	RESULTS.
1 c.c. glycocoll		+ 1 drop ninhydrin and heat	+++++
1 c.c. "	+ 1 drop n/50 oxalic	+ 1 " " " "	++++
1 c.c. "	+ 2 drops " "	+ 1 " " " "	+++
1 c.c. "	+ 3 " " "	+ 1 " " " "	++
1 c.c. "	+ 4 " " "	+ 1 " " " "	+
1 c.c. "	+ 5 " " "	+ 1 " " " "	—

Experiment VI was performed to determine the effect of dilute sodium hydroxide, using n/10 sodium hydroxide.

TABLE X.

GLYCOCOLL (1-1,000).	N/10 NaOH.	1% NINHYDRIN.	RESULTS.
1 c.c. glycocoll	—	+ 1 drop ninhydrin and heat	+++++
1 c.c. "	+ 1 drop N/10 NaoH	+ 1 " " " "	++++
1 c.c. "	+ 2 drops " "	+ 1 " " " "	+++
1 c.c. "	+ 3 " " "	+ 1 " " " "	++
1 c.c. "	+ 4 " " "	+ 1 " " " "	+
1 c.c. "	+ 5 " " "	+ 1 " " " "	+
1 c.c. "	+ 6 " " "	+ 1 " " " "	—

The results of these experiments indicate that N/10 sodium hydroxide interferes with the ninhydrin color reaction to about the same extent as equal amounts of N/50 oxalic acid and as N/100 hydrochloric acid and that small amounts of weak acids and alkalies hinder or prevent this color reaction.

Some experiments were tried to see if sodium chloride interfered with or lessened the delicacy of the reaction.

Experiment VII, using 20% Sodium Chloride.

TABLE XI.

1 c.c. NaCl	+ 1 drop glycocoll	+ 1 drop ninhydrin and heat	—
1 c.c. "	+ 2 drops "	+ 1 " " " "	+
1 c.c. "	+ 4 " "	+ 1 " " " "	+
1 c.c. "	+ 6 " "	+ 1 " " " "	+

controlled with water

TABLE XII.

1 c.c. water	+ 1 drop glycocoll	+ 1 drop ninhydrin and heat	—
1 c.c. "	+ 2 drops "	+ 1 " " " "	+
1 c.c. "	+ 4 " "	+ 1 " " " "	+ + +
1 c.c. "	+ 6 " "	+ 1 " " " "	+ + + + +

The above experiment was repeated using one per cent sodium chloride and heating in the oil bath three and one-half minutes instead of two.

TABLE XIII.

1% SODIUM CHLORIDE.	GLYCOCOLL (1-1,000).	1% NINHYDRIN.	RESULTS.
1 c.c. NaCl	+ 2 drops glycocoll	+ 1 drop ninhydrin and heat	—
1 c.c. "	+ 4 " "	+ 1 " " " "	+
1 c.c. "	+ 6 " "	+ 1 " " " "	+ + +
1 c.c. "	+ 8 " "	+ 1 " " " "	+ + + +

controlled with water

TABLE XIV.

1 c.c. water	+ 2 drops glycocoll	+ 1 drop ninhydrin and heat	+
1 c.c. "	+ 4 " "	+ 1 " " " "	+ +
1 c.c. "	+ 6 " "	+ 1 " " " "	+ + + +
1 c.c. "	+ 8 " "	+ 1 " " " "	+ + + + +

This experiment was repeated using 5% Sodium Chloride.

TABLE XV.

5% NaCl.	GLYCOCOLL (1-1,000).	1% NINHYDRIN.	RESULTS.
1 c.c. NaCl	+ 2 drops glycocoll	+ 1 drop ninhydrin and heat	—
1 c.c. "	+ 4 " "	+ 1 " " " "	+ +
1 c.c. "	+ 6 " "	+ 1 " " " "	+ + +
1 c.c. "	+ 8 " "	+ 1 " " " "	+ + + + +

This experiment was repeated using 10% Sodium Chloride.

TABLE XVI.

10% NaCl.	GLYCOCOLL (1-1,000).	1% NINHYDRIN.	RESULTS.
1 c.c. NaCl	+ 2 drops glycocoll	+ 1 drop ninhydrin and heat	+
1 c.c. "	+ 4 " "	+ 1 " " " "	+
1 c.c. "	+ 6 " "	+ 1 " " " "	+ +
1 c.c. "	+ 8 " "	+ 1 " " " "	+ + +

These experiments indicate that sodium chloride lessens the intensity of the color reaction and gives a lighter and more violet color; and that sodium chloride diminishes slightly the delicacy of the reaction.

We had noticed in some of the preceding experiments that prolonging the time of heating gave much better color reaction and these experiments were per-

formed to determine the effect of a longer heating period. One or two drops of glycocoll (1-1,000) were added to 1 c.c. of water, then ninhydrin was added and heated in the oil bath as before for the time indicated.

TABLE XVII.

	2 MINS.	5 MINS.	7.5 MINS.	10 MINS.	12.5 MINS.	15 MINS.
2 drops glycocoll	—	+	+++	++++	+++++	++++++
1 drop "	—	—	+	++	+++	+++++

Temperature of bath was raised from 120° to 125° C.

1 drop glycocoll	—	+	++	+++	+++++	+++++

These experiments indicate that one gets a much better test by prolonging the time of heating and wherever there is no objection to this, it gives much better results.

Ninhydrin will give a positive reaction with glycocoll in dilution of (1-15,000) when heated two minutes and will give a positive reaction in dilution of (1-45,000) when heated twelve minutes.

Some of the preceding experiments were repeated and the heating in the oil bath continued for twelve minutes instead of two and the temperature kept at 120° C. as in the preceding experiments.

TABLE XVIII.

NINHYDRIN REACTION. ++	RESULTS (1-100).	RESULTS (1-1,000).	RESULTS (1-10,000).
Casein poison	+++	++++	+
Colon poison	+++	++++	++
Tuberculosis cell poison	++	+++	+
Dog's liver poison	+++	++++	+
Beef's kidney poison	+++	++++	+
Casein	+++++	++++	+
Colon cell substance	+++++	++++	++
Tuberculosis germ substance	+++++	++++	+
Egg albumen	+++++	+++	—
Peptone	+++++	++++	+
Colon residue[4]	—	—	—
Tuberculosis cell residue	—	—	—
Casein residue	—	—	—

The above suspensions were all carefully neutralized before the experiments. In these experiments the cell substance and the protein poison derived therefrom give positive ninhydrin color test in dilutions of (1-10,000) except egg albumen, which was positive in dilutions of (1-5,000), while the three residues[4] tested were negative in dilutions of (1-100).

The question naturally arises here; is the ninhydrin reacting substance present in the protein poison or is it cleaved by the heating for twelve minutes?

Early in this investigation, when performing the ninhydrin tests, the solution was heated for two minutes and we got only slight tests with the protein poison in dilutions of (1-100); it was found that keeping the solution either in acid or alkaline solutions at room temperature for two to four days, and then neutralizing and testing gave very much stronger tests, deeper colors. This in-

dicates that there is some cleaving of the protein poison and part, at least, of the ninhydrin reaction is due to it.

The toxicity of the protein poison after heating in the oil bath at 120° for twelve minutes was not appreciably diminished.

CONCLUSIONS.

1. Vaughan's portein poisons in dilutions up to (1-10,000) gives the ninhydrin reaction.

2. The proteins from which the poisons are obtained will also give the ninhydrin reactions in dilutions up to (1-10,000).

3. The cell residue in dilutions of (1-100) does not give the ninhydrin reaction.

4. Dilute acids and alkalies interfere with this reaction.

5. Sodium chloride interferes very slightly with the reaction.

6. Prolonging the time of heating makes the reaction very much more delicate.

BIBLIOGRAPHY.

[1]Vaughan's Protein-Split Products, p. 98.
[2]Riehemans: Jour. Chem. Soc., vol. xcvii, 1910-2025.
[3]Abderhalden and Schmidt: Zeit. fur Physiol. Chem., vol. lxxii, 1910-1937.
[4]Vaughan's Protein-Split Products, p. 165.

THE BULGARIAN BACILLUS IN THE TREATMENT OF VULVOVAGINITIS*

By Milton B. Cohen, M.D., Cincinnati, Ohio.

OF the many problems which have been studied both by clinicians and laboratory men, one of the most interesting is that of combatting infections which have become chronic and in which the parasite seems to have established a resistance to the immunizing substances of the host. One of the methods which has been used to treat such infections is the implantation upon the infected surface of some organism which in cultures produces biologic products capable of destroying the infecting organism or inhibiting its growth. This method of symbiosis has been applied with some success to the treatment of diphtheria carriers by Catlin, Scott and Day[1], and others, and is used more or less as a routine in many hospitals for contagious diseases.

At the Cincinnati General Hospital, a number of investigators have been interested in the subject of vulvovaginitis in children, especially in that form which is usually spoken of as gonorrheal, from which organisms morphologically and culturally indistinguishable from the gonococcus can be isolated. The problem of prophylaxis and treatment of this disease is a very important one as many of the infected children are never completely cured and the cures which are reported are secured only after very energetic and persistent treatment

*From the Pathologic Institute of the Cincinnati General Hospital, and the Department of Pathology of the University of Cincinnati.

with a variety of local injections and irrigations alone or combined with vaccine therapy. In many cases it requires from several months to a year or more to effect a probable cure and frequently after the child is dismissed and treatment is discontinued, the disease recurs. It seems that these vaginitis cases may be included in the carrier group, in which the infecting organisms live and multiply in foci which cannot be reached by the usual methods of treatment. It therefore seemed that it might be possible to implant in the vagina a harmless organism which would thrive in the crypts and folds and so alter the vaginal secretion by its metabolism as to render it no longer suitable for the growth of the gonococcus.

In looking through the literature on the subject, one can find but one reference to such a treatment. Taussig[2] tried the effect of suppositories of Bulgarian bacilli made from tablets prepared by Parke, Davis & Co. He introduced these into the vagina three times weekly continuing the treatment for from six to eight weeks. Three of his cases improved. There was no attempt made to find out whether or not the Bulgarian bacillus *per se* was responsible for the improvement. Rosenthal[3], working in Hayem's laboratory, did a number of symbiotic cultural experiments with this organism and numerous other bacteria among them the meningococcus. He concluded that the metabolic products of the Bulgarian bacillus were very antagonistic to organisms of the meningococcus group, to which the gonococcus belongs.

With this information at hand, it became important to determine whether the Bulgarian bacillus would grow in the human vagina, and whether, when grown there, it would cause the death of the gonoccus or inhibit its growth.

Strains of this organisms were obtained from Parke, Davis & Co., from the Bulgarian Bacillus Products Co., from the stomach contents of a case of gastric carcinoma, and from normal human saliva. After several trials, the following method was adopted as a routine. The centrifuged sediment from a mixed culture of these four strains grown for 48 hours at 37.5° in whey, was mixed with 5 per cent lactose solution. This solution was injected intravaginally twice daily by means of a Luer syringe and a special glass tip which, when inserted through the hymen, plugged the opening and allowed the vagina to be completely filled and the solution to come into contact with its entire surface. During this experiment, all other treatment was discontinued.

Three cases were treated by this method. Each one had a very profuse discharge in which gonococcus-like organisms could be easily demonstrated in smears taken by the swab method. Smears from the vagina were examined twice weekly for the presence of Bulgarian bacilli and gonococcus-like organisms. Not once was the Bulgarian bacillus demonstrated in direct smear even when it was taken within twelve hours after an injection. In two cases, after ten and thirteen days of treatment respectively, the discharge ceased and no gonococci could be found in the vaginal smears. The treatment was discontinued for two days during which time Bulgarian bacilli were demonstrated with some difficulty in cultures from the vagina using the glacial acetic acid method described by Heinemann and Hefferman.[4] On the morning of the third day a discharge reappeared in which gonococcus-like organisms could be shown. Treatment, using the culture which had been isolated from the vagina two days

previously, was resumed and was continued for three weeks. During this time several negative slides were obtained, but almost always after sufficient search a few typical gonococci could be found. The third case developed measles on the eighth day of treatment and was transferred to the hospital for contagious diseases where the vaginitis was not treated. On the thirteenth day after developing measles, smears made from the vagina were positive for gonococcus-like organisms and negative for Bulgarian bacilli. The bacillus was demonstrated in small numbers by cultural methods.

Although the number of cases treated is very small, and the length of treatment short, it seems that the following conclusions are justified.

1. The Bacillus bulgaricus does not thrive in the human vagina and is therefore of little use in the treatment of vulvovaginitis.

2. The results obtained by Taussig in his three cases were probably not due to the Bulgarian bacillus.

I wish to express my sincere thanks and appreciation to Drs. P. G. Wooley, W. B. Wherry and Wade W. Oliver, for their valuable suggestions and assistance.

BIBLIOGRAPHY.

[1]Catlin, Scott and Day: Jour. Amer. Med. Asso., Chicago, 1911, lv, 1452.
[2]Taussig, F. J.: Am. Jour. Med. Sc., 1914, cxlviii, 480.
[3]Rosenthal, G.: Seances et Memoires de la soc. de Biologie, Paris, 1910, v, 68.
[4]Heinemann, P. G., and Hefferman (Mary): Jour. Infect. Dis., 1909, vi, 304.

LABORATORY METHODS

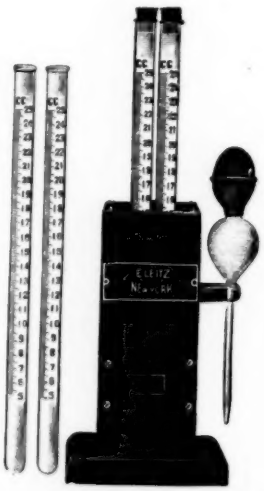
A SIMPLE COLORIMETER FOR CLINICAL PURPOSES*

By Victor C. Myers, New York City.

ON account of the European war it is very difficult at the present time to secure the excellent colorimeters manufactured by Duboscq and by Hellige. Furthermore, even in normal times these instruments are comparatively expensive on account of their type of construction.

To supply the need for a simple, relatively accurate but inexpensive colorimeter for clinical purposes, the instrument described below has been devised. The instrument is similar in principle to the Sahli hemoglobinometer, but considerably larger. With it one may make such estimations as the excretion of phenolsulphonephthalein in the urine and the uric acid, urea, creatinine and sugar in the blood, etc., with a sufficient degree of accuracy for any clinical purpose.

The instrument illustrated above consists of a box containing two tubes of identical bore (1.2x26 cm.) graduated in tenths from 5 to 25 c.c. The tubes are placed side by side in the instrument, colorimetric comparison being made in the ungraduated portion (0-5 c.c.) through an opening 1x2.2 cm. against a white glass background. To make a colorimetric determination it is simply necessary to dilute the solution in one of the tubes, preferably the unknown, until the depth of color is identical with the other tube. The diluting fluid, generally water, is added with the diluting pipette, inverting the tube after each addition.



*From the Laboratory of Pathological Chemistry, New York Post-Graduate Medical School and Hospital.

For standards one can best employ solutions of the substance to be determined, i. e., phenolsulphonephthalein, uric acid, nitrogen in form of ammonium sulphate or chloride, creatinine in saturated picric acid solution and glucose in saturated picric acid solution, developing the color in the standard simultaneously with the unknown. Our experience would indicate that for colorimetric work there are no standards quite as satisfactory as those prepared from the substance to be determined and treated in the same way as the unknown.

The calculations with the instrument may be made very simple. If, for example, a blood sugar estimation is being made and the standard glucose solution is the equivalent of 0.1 per cent blood sugar for the conditions used, then a dilution of the unknown to 15 c.c. would represent 0.15 per cent blood sugar, etc.

A POSITIVE TEST FOR BLOOD IN THE STOMACH*

By Max B. Leviton, S.B., M.D., Chicago, Ill.

THE test for blood here described is probably more delicate and exact than any hitherto proposed in that the red cells can be seen by direct inspection of the centrifuged fluid under the microscope. It is a modification of Loeper and Binet's[1] test of gastric contents (washings of the empty stomach), except that there is no preliminary lavage and the contents are first neutralized to avoid laking of the blood cells.

The technic is as follows:

The patient is directed to omit anything for breakfast, including liquids, to rinse the mouth and teeth frequently and expectorate any saliva that might form, so that little or none of the cellular elements of the buccal cavity might be swallowed (epithelium, pus cells, blood, etc.). A half glass of water containing a dram of sodium bicarbonate is administered, with a glass of saline solution a few minutes later. The abdomen is then thoroughly massaged and gently squeezed for a few minutes and the contents aspirated by means of a glass irrigating syringe attached to a narrow caliber colon tube (15 French), 4 mm. in diameter. This soft tube produces no trauma as when the ordinary aspirating tube is used and therefore the red cells seen are actually from the stomach. Three small extra holes made in the tube, as kindly suggested to me by Prof. Bird M. Linnell, of Rush Medical College, allows aspiration without a suction action on the mucosa, which is of itself likely to produce bleeding. Precautions should be taken to have connections tight, so that the tube is not swallowed. It is usually necessary to assist the passage of the soft tube down the pharynx by pushing it down with one finger in the mouth to prevent kinking. For this purpose it is better to wear a thick rubber glove to avoid abrasions of the hand on the teeth. The patient assists by swallowing.

All that is necessary is one syringeful, which is centrifuged and examined

*From the Medical Clinic of Rush Medical College, Chicago, Ill.
[1]Presse Medicale, Apr. 8, 1914.

microscopically. It is better to wipe the mucus off the end of the tube and expel a few drops before ejecting the fluid from the syringe for examination.

Tests showed that even in concentrated soda solution the red cells remained comparatively unharmed for a long time. The contents that were analyzed up to date almost always showed several red cells, and it is questionable whether under these conditions there are not nearly always a very few erythrocytes in the normal stomach.

The test, therefore, is useful when considered quantitatively, say approximately more than three or four to the high power field. In addition, the other findings suggested by previous writers might be employed, i.e., pus cells, fragments of mucosa, tumor cells, Wolf Junghans' test for dissolved albumin, and lactic acid, besides Oppler-Boas bacilli, yeasts and sarcinæ.

The ordinary coarse tube sometimes brings up blood, especially in the mucus surrounding the opening. As a supplementary test when other findings have proved equivocal, or in sensitive patients who will not take the larger tube this test might prove of some use. Since microscopic bleeding occurs in some cases of gastritis, so-called hemorrhagic erosions, etc., *it is especially valuable as a negative test for blood.*

Special thanks are due to Dr. R. Berghoff, of Central Free Dispensary, Rush Medical College, for many courtesies and the use of cases.

The Journal of Laboratory and Clinical Medicine

VOL. I. JULY, 1916 No. 10

Editor-in-Chief: VICTOR C. VAUGHAN, M.D.
Ann Arbor, Mich.

ASSOCIATE EDITORS

DENNIS E. JACKSON, M.D. - - ST. LOUIS
HANS ZINSSER, M.D. - - - NEW YORK
PAUL G. WOOLLEY, M.D. - - CINCINNATI
FREDERICK P. GAY, M.D. - - BERKELEY, CAL.
J. J. R. MACLEOD, M.D. - - - CLEVELAND
ROY G. PEARCE, M.D. - - - - CHICAGO
ROGER S. MORRIS, M.D. - - CINCINNATI

Contents of this Journal Copyright, 1916, by The C. V. Mosby Company—All Rights Reserved
Entered at the Post Office at St. Louis, Mo., as Second-Class Matter

EDITORIALS

Gastrointestinal Diseases

WHAT we call gastrointestinal diseases are expressions of alterations of function in one or more parts of the gastrointestinal system. They are commonly confused with symptoms, such as hyperacidity, hypoacidity, hypermotility and hypomotility, which are not diseases, but symptoms of disease. Sometimes they are associated with symptoms in other parts of the body than the gastrointestinal tract, and such symptoms call attention to the fact that the various organs of the body are not truly separated or independent, but that they are actually dependent upon one another. So with gastrointestinal upsets the nervous system may be affected, or the urinary system, and it is from these distance effects that we have come to make so much of a group of symptoms, which may be combined into different complexes, in different individuals, which we call, comprehensively, gastrointestinal intoxications or, also, autointoxications.

In order to be clear in our conceptions we should consider first of all the functions of the organs comprising this tract or system.

The function of the stomach and of the intestines also is to contain and retain food for a certain period of time during which the food is chemically changed

by means of ferments. In order to fulfill this function it must be capable of expansion, and, in order to expel the contents at the proper time it must be capable of returning to its original size. In other words, it must be elastic and contractile, and the elasticity and contractility are chiefly the result of the condition of the musculature. The function of the intestine is to carry the food from the stomach to the external world and at the same time to allow time for absorption of foodstuffs into the body. This function depends upon elasticity and contractility and here again the contractility is mainly dependent upon the condition of the musculature. In other words, the function of the gastrointestinal tract, so far as motility (contractility) is concerned, is dependent upon the condition of the muscularis, and so *disease tends to be produced by variation in the elasticity and motility of the various portions of the gastrointestinal tract.*

It is these qualities of elasticity and contractility which prevent stasis in the intestinal tract. Normally the various segments of the tract act in such harmony that the contents are gradually pushed along to their normal destination in a certain normal time. A healthy bowel will not permit of stasis but will carry on its motor functions with ease and regularity. To assist in this function there must be a coordinating or regulating mechanism. This Keith believes he has found in the myenteric (Auerbach's) plexus. He finds that at certain points this plexus is concentrated to form masses (or nodes) which correspond to the nodes in the conducting tissue of the heart, and that at these nodes new rates of peristalsis are inaugurated and persist throughout the segment to which they belong. Evidently *disease of the gastrointestinal tract may occur because of interference with, or damage to, the myenteric coordinating system.*

In order that the food shall be properly prepared for absorption, the necessary kinds and amounts of ferments must be secreted by the glands of the gastrointestinal tract and by the accessory glands, and in order that these shall act properly the contents of the tract must have the proper chemical reaction. In the stomach the reaction must be acid; in the intestine it must be alkaline. Therefore *variations in the quantitative secretion of the various digestive fluids and in the qualitative composition of them, tends to produce disease.*

Gastrointestinal disease arises from abnormal changes in elasticity, motility (contractility), segmental coordination, secretion of ferments, and (chiefly) chemical reaction.

When we consider these four groups we find that we can most usefully combine them into two large groups, for we find that changes in elasticity and motility are apt to occur together; and that changes in production of ferments and the chemical reaction of the juices are apt to be combined. Also we discover that each of these groups are interwoven to such an extent that it is not possible to separate them completely.

The normal course of events in gastric digestion is briefly as follows:

Food enters the stomach and is there kneaded and thoroughly mixed with gastric juice so that the ferments, chiefly pepsin, may act upon the proteins. For the ferment action, a certain degree of acidity is necessary. After a certain time the partially digested food is expelled through the pylorus and enters the duodenum.

What we call gastric indigestion may depend upon a break at any point in

this process, i.e., the muscular movements of the stomach may not be sufficiently active to produce thorough mixture of the food and the gastric juice; the gastric juice may not contain sufficient pepsin to accomplish a normal result; the acid content of the gastric juice may be below or above normal, and then in either case the food may be held too long in the stomach and then undergo abnormal changes which lead to more or less disturbing symptoms or distress.

How shall we account for variations in gastric motility? There is a variation that occurs normally and which depends upon the nature of the ingested food. For instance, carbohydrate foods pass through the stomach most rapidly, proteins are next and fats are slowest. We can say at once then, that a diet very rich in fats will hinder the passage of foods through the stomach. Moreover the ingestion of oils decreases the amount of gastric juice, while ingestion of proteins increases it, and carbohydrates (bread) produce a juice of greatest digestive power. These facts account for the ordinary effects of dietary indiscretions which are commonly transient, but which may persist, if the indiscretions are persisted in, and produce other less transient effects resulting in structural changes.

Now it is quite possible that these normal variations in motility are the result of modification in the acid content of the gastric juice. We know the opening and closing of the pylorus are due to the reaction of the food, i.e., they depend upon the presence of a certain amount of free acid. We know that ingestion of carbohydrates produces an abundant active secretion, and we know that carbohydrates are less active in neutralizing the acid (by chemical combination) than the proteins which also produce an abundant secretion. We would expect then, that the carbohydrates would pass through the stomach more rapidly because they permit the acid to accumulate, and that the proteins would remain longer in the stomach because in combining with the acid they reduce the acidity of the gastric contents. Fats and oils, on the other hand, reduce the quantity of juice and therefore the acid is slow in accumulating.

When the emptying of the stomach is unduly impeded, there is opportunity for fermentation to occur in the contents. We constantly swallow bacteria with our food, but commonly these organisms are rendered harmless because their activities are hindered by the hydrochloric acid. With a decrease of acid they are allowed to act upon the food, and in doing this they produce abnormal acids and gases. The former act upon the mucous membrane producing inflammatory effects; the latter produce distension or "bloating."

Immediately inflammation is produced, an increased amount of mucus is produced, and mucus, being alkaline in reaction, neutralizes more hydrochloric acid, and therefore assists in hindering the passage of food into the intestine. The same stimulation which produces the increase in mucus, irritates the functional cells, so that eventually they become fatigued and produce less secretion. The result of this is that further fermentations are assisted and so (the disease we call it) becomes chronic. When this stage is reached—when inflammation has become chronic, fibrous tissue is produced in the wall of the stomach, the functional cells atrophy and disappear, the mucous membrane becomes thin and gradually becomes less and less able to produce the necessary amount of acid or ferments. When this stage is reached, an incurable condition has been pro-

duced. Before it is reached, there is no incurable stage,—only each more advanced stage is less easily remedied.

But oftentimes it is not so much the relative amounts of carbohydrates, proteins, or fats that is the original cause of indigestion. More frequently it is the quality of the food or other substances that gain entrance to the stomach. Very hot food or drink, very cold drinks, alcoholic beverages, highly spiced foods—all are far more frequent causes. These act by the virtue of their irritative action on the mucous membrane. They produce hypersecretion of mucus and the related stages of fermentation that have already been mentioned, or they cause hypersecretion of gastric juice with subsequent atrophy or hypertrophy of the mucous membrane, resulting on the one hand in absence of secretion or, on the other, in more or less permanent hypersecretion.

What has been said concerning the stomach applies with very few variations to the intestines. Changes in motility, in secretion and absorption depend largely upon factors which are introduced from without, and very commonly are associated with gastric disturbances. Gastric fermentations are prone to lead to intestinal disease, and variations in gastric acidity lead to modifications in the production of pancreatic ferments. In the course of these general modifications which result from gastrointestinal disease then are produced the most various diseased conditions in other organs which cause the symptoms which belong to what we often call the gastrointestinal intoxications.

But all gastrointestinal disease does not depend upon abnormal processes which are primary in the stomach and intestines. Some are the results of changes which are primary in the liver or in the pancreas. As a result of certain changes, quantitative or qualitative variations in the secretions of these organs are produced, and these variations are of far-reaching importance.

It will be remembered that all the above-mentioned juices are poured into the intestine, immediately after the entrance of the acid gastric chyme into the duodenum apparently as a result of the action of the acid. All the intestinal secretions are alkaline. They therefore tend to neutralize the acid of the gastric juice and therefore they produce the conditions which are necessary for opening of the pylorus. So long as the duodenal contents are acid, the pylorus remains closed. An *insufficient amount of alkaline juice from the digestive glands tends to produce disease.*

The activity of the pancreatic juice depends upon the activation of its proteolytic pro-enzymes by enterokinase which exists in the succus entericus, which is caused to flow by the presence of pancreatic juice in the intestines. *Absence of enterokinase tends to produce disease.*

The flow of all the intestinal juices, pancreatic, bile and succus entericus, is brought about by the action of the secretion (produced in the cells of the intestines by the action of the acid gastric chyme) upon the cells of the pancreas, liver, and intestinal glands. *Absence of sufficient acid in the gastric juice tends to produce lack of intestinal secretion, and hence to produce intestinal disease.*

If the pancreatic juice is not activated, proteolytic digestion suffers. If the bile is not present in sufficient amounts, the utilization of the fats of the food is reduced or hindered. The conditions produced in this way are ones that result from insufficient preparation and absorption of food. The insufficient preparation allows of increased bacterial activity and tends to the production of abnor-

mal substances, or substances in abnormal amounts, which, being absorbed, may give rise to intoxications, providing they are not neutralized.

But aside from these there are changes which occur in the glandular organs themselves which produce similar effects. Diseases of the liver, of the pancreas, of the wall of the intestines, produce the same effects. In this group we have the fibroses of the liver and the bile passages which decrease the flow of bile and produce qualitative changes in it. Inflammation of the pancreas or its ducts produces quantitative and qualitative effects upon the pancreatic juice and similar changes in the wall of the intestines tend to reduce the formation of enterokinase and secretin.

Just as gastrointestinal disease may have its starting point outside that tract, in the accessory glands in the abdominal cavity, so also it may have its origin in the mouth. The mouth is the most important portal of infection of the body, and is perhaps more prone, especially in the years after the first decennium, to infection than any other part of the body. Moreover diseases of the mouth, especially those in which the teeth are involved, are every day assuming greater importance in medicine. It is becoming more and more evident that the lesions of many accepted clinical complexes are secondary to primary infections of the oral cavity and also that many obscure symptoms are the sequels of chronic focal infections which in very many cases are located in the teeth or in their surrounding tissues. Hence it is that pyorrhea alveolaris and peridental and dental abscesses are becoming of as great importance to the physician as to the dentist, and that there is every reason to believe that, in certain directions at least, the practice of dentistry will have to be revolutionized even as medical views concerning the importance of the mouth as a source of generalized disease are being changed. It is coming to be realized that foci of infection in or about the mouth may be the starting points of such so-called diseases as rheumatism, endocarditis, appendicitis, gall-bladder disease, gastric ulcer, osteomyelitis, hay fever, asthma, urticaria, and even certain goiters. When we say in or about the mouth we have reference to the tonsils, the nasal sinuses and antra, as well as the teeth and peridental tissues.

The reason why the mouth is so apt to be a primary source of trouble is that it, more than almost any other part of the body, is opposed to the action of external injuries, and that modern habits of eating and drinking produce conditions which, without proper precautions, lay the foundations for various sorts of local and general trouble. Too hot or too cold foods taken into the mouth do two things;—they injure the epithelial surfaces and so predispose to infection, and they tend to damage the teeth and make them more easily attacked by bacteria. Food which is too carefully chosen for tenderness and easy mastication, or which is finely divided, tends to collect between the teeth or along the margins of the gums, and there ferment. Thereupon inflammations or caries, or both, result. The more antique habit of not eating hash but of exercising the teeth and gums on the food made the toothbrush less essential for health than it now is. Cattle which are fed on soft food,—as, for instance, still slops,—almost exclusively, have dental trouble that animals under normal circumstances never have. It is exercise which keeps the teeth and gums in good condition and if this cannot be accomplished by means of the food, some other agent is required and this is usually the toothbrush assisted too frequently by the dentist's drill. Den-

tal floss takes the place of the older meat fibers which stuck between the teeth and had to be picked out after the prandial exercises (or even sometimes during them). In this process the spaces between the teeth were cleaned.

From the standpoint of dentistry it is important to remember that crowns and bridge-work, as they are too commonly applied, while they may be something of a convenience, are nevertheless a very real danger in producing focal and general infections and intoxications. To the truth of this x-ray pictures of the teeth will testify. Any apparatus which tends to produce mechanical irritation is a dangerous one, for while it is true that foreign bodies may produce little or no damage provided they exist in aseptic surroundings, yet in the presence of infective organisms they act invariably to intensify the reaction between tissue and germ. A bridge which offers opportunity for the collection of food and bacteria about it; a crown or a bridge which is attached to or which covers a tooth whose nerve has been killed (by which procedure the tooth itself has been made a foreign body), especially if complete sterilization has not been carried out, is a menace to the general health of the patient, who had far better have fewer teeth than such an appliance. A little macerated pulp at the bottom of root canal and one living bacterium buried at the bottom of a root canal under an impervious cap or filling, is not to be preferred to a vacant space in the tooth line. It is under such conditions that root and alveolar abscesses develop and remain for long periods of time affecting the health of the individual by producing bacteria and toxins to enter the blood stream by which they are carried to the heart, central nervous system, muscles, bones, or other tissues and organs.

BIBLIOGRAPHY.

Pawlow: The Work of the Digestive Glands, London, 1910.
Cannon: The Mechanical Factors of Digestion, New York, 1911.
Starling: Human Physiology, Phila., 1912.
Krehl-Hewlett: Clinical Pathology, Phila., 1907.
Davis: Intestinal Obstruction: Formation and Absorption of Toxin, Bull. Johns Hopkins Hosp., 1914, xv, 33.
Keith: Lancet, London, 1915, ii, 371; Brit. Jour. Surg., 1915, ii, 576.
Gilmer and Moody: A Study of the Bacteriology of Alveolar Abscess and Infected Root Canals, Jour. Amer. Med. Assn., 1914, lxiii, 2023.
Billings, Mayo, and Rosenow: Mouth Infection as a Source of Systemic Disease, Ibid., 2024-2027.
Craig: Peridental Infection as a Causative Factor in Nervous Diseases, Ibid., 2027.
Evans and Middleton: Endamebic Pyorrhœa and Its Complications, Jour. Amer. Med. Assn., 1915, lxiv, 442.
Bass and Johns: Pyorrhœa Dentalis and Alveolaris, Ibid., 553.
Hunter: Severest Anæmias; Their Infectious Natures, etc., London, 1909.
Hunter: Oral Sepsis, Brit. Jour. Dent. Sc., 1914, lxii, 833.
Turner: Dental Sepsis, Brit. Med. Jour., 1914, i, 1244; 1301.
Collins: The Possible Relationship of Organic Disease of the Nervous System to Rigg's Disease, Tr. Assoc. Amer. Phys., 1913, xxviii, 87.
Gies: Dental Cosmos, 1915, lvii, 276.

—*P. G. W.*

Death by Strangulation

MEDICO-LEGALLY it is desirable to distinguish between hanging and strangulation, because most of the cases of hanging which the expert is called upon to investigate are suicidal; while death from strangulation is generally homicidal. Strangulation is defined by Tardieu as "an act of violence

in which constriction is applied directly to the neck, either around it or in the fore part, so as to prevent the passage of air and thereby suddenly suspending respiration and life." As has been pointed out by Taylor, this definition includes hanging, but as the same author goes on to say, "while there is only one method of producing death by hanging, there are various methods of producing death from strangulation. A person may be strangled by the use of a cord, band, or ligature drawn tightly around the neck, or by manual violence to the front of the neck, whereby respiration is prevented."

Suicidal strangulation is possible, but is exceedingly rare. The question has been asked many times whether or not it would be possible for one to compress his own windpipe to the extent of inducing death. On the negative of this question it is argued that as soon as the period of unconsciousness is reached, —possibly before this time—the fingers will lose their power of compression, air will again pass through the larynx, and death will not result. This argument is probably correct, but it would be possible for a person to pass a cord a number of times around his neck and then by pulling on both ends kill himself, because, on account of the number of coils, the pressure would not be relieved when the hands ceased to pull. Indeed, cases of suicide by strangulation in this way have been reported. Another method of suiciding by strangulation is to pass a cord around the neck, then put a stick of some kind between the cord and the neck, and twist the stick. Several cases of suicide by this method have been recorded. Possibly there are other maneuvers which might be resorted to with success in the accomplishment of this purpose. However, unless there be some direct and positive evidence that the act has been self-committed, it is to be presumed that death from strangulation is homicidal. It is very easy for a strong man to so compress the larynx of a child or a woman with his fingers as to prevent any cry for help, and to induce death within a few minutes. In fact this method which has been resorted to for the purpose of robbery and murder, is so well known that a special name has been given to it, and it is designated as the crime of "garroting" on account of its resemblance to the Spanish method of executing criminals. The garrot consists of a brass collar, which is placed about the neck and gradually tightened by a screw behind. This screw has a sharp point and it not only tightens the collar but pierces the spine.

When death has been caused by strangulation with the hands there are usually external marks to indicate the nature of the injury. In fact the murderer who employs this method generally uses more violence than is necessary. He frequently tears the flesh with his nails, bruises the soft tissue, and in many instances crushes the cartilaginous structure of the larynx. In some instances the injury thus done is so great that it is quite evident that it could not be self-inflicted. Frequently the hyoid bone is fractured. In a case of this kind Schüppel proved that death had been thus caused in the body of a child aged ten who was found in the debris of a burned building.

Homicidal strangulation may be accomplished by the powerful hand of the murderer or by means of a cord or rope. When something is placed about the neck, and death is induced by tightening or twisting this, the victim usually struggles sufficiently to produce evidences of violence. When the cord is small

it may cut the neck deeply, and indeed this may be accomplished when a handkerchief is used for strangulation by bringing the constriction to bear solely upon one hem or by twisting the handkerchief and thus converting it into a cord. In some rare instances where death has been induced by strangulation, the murderer has attempted to make it appear that the injury has been self-inflicted, but usually these attempts overstep themselves, and aid in detecting the crime. Sometimes the medical expert is asked whether death was caused by strangulation or induced in some other way, and the injury to the neck inflicted subsequently. This question is not always easy to answer. So far as external appearances are concerned, the presence of ecchymoses on the neck, protrusion of the eyeballs and of the tongue, together with a livid, swollen appearance of the face, constitute marked indications of death from strangulation. However, Caspar has pointed out that a ligature applied about the neck within an hour or two after death may cause ecchymoses which cannot be distinguished from those produced during life, and there may be protrusion of the eyes, lividity and swelling of the face and extrusion of the tongue in death from other causes. So far as evidence furnished by postmortem examination is concerned, it may be stated that this may be of the greatest value. As a rule the lungs are congested and some of the more superficial of the air cells may be ruptured, leading to a more or less extensive emphysema, and giving to the surface of the lungs a mottled appearance with patches covered with thin white layers of tissue from which when punctured air escapes. While this is the usual condition after death from strangulation, it is not constant. When present and accompanied by evidences of external violence applied to the neck, the proof of death by strangulation is positive, but when absent we cannot say that death has not been caused by strangulation. Moreover postmortem examinations in these cases are frequently not made until after many days, and putrefactive changes may be such as to confuse the most experienced expert. After death from strangulation the heart presents no constant or uniform condition, although it generally contains fluid blood, and the right side is more prominently distended than the left. The brain is congested, as it is in most all cases of death from asphyxia.

When the expert is called upon to examine a body supposed to have been strangled he must make most careful examination, not only of the neck, but of every part of the surface for evidences of external violence. He should give attention to the limbs, especially the legs, wrists and arms. The murderer is likely to hold the hands of his victim, or to throw him by striking his feet from under him. In garroting, the murderer frequently presses upon the chest of his victim, sometimes upon the abdomen. It not infrequently happens that on account of such pressure vomiting results, and after death vomited matters may be found in the pharynx, and even in the larynx. In case the victim is a female, evidences of injury to the sexual organs should be sought for and any other indications of rape should not be overlooked. If wounds be found the question arises as to whether it would be possible for them to be accidental or self-inflicted. In many cases of death from strangulation it is well to examine the stomach for poisons, especially those of narcotic action, inasmuch as the homicide sometimes resorts to these for the purpose of rendering his victim help-

less. The presence of a cord or rope about the neck should not always be considered proof that death has resulted from either strangulation or hanging. There are several cases upon record in which the murderer after accomplishing his purpose in some other way has placed a rope or a cord about the neck of his victim in order to make it appear that death by hanging had been self-inflicted.

Strangulation With a Cord.—The word cord is used here, to mean anything that is long enough and pliable enough to be twisted about the neck. The things used in strangulation are almost as diverse, probably not quite so, as in hanging. There is this fundamental difference between hanging and cord strangulation, in the former the force that compresses the neck and causes death is the weight of the body, fully or only partially applied, while in the latter the weight of the body is in no way concerned and the active force is that used in tightening the cord about the neck and is exerted through the hands of the suicide or the murderer as the case may be. As a rule, in hanging the cord is placed directly under the chin, above the larynx or over its upper portion and between the thyroid cartilage and the hyoid bone. In strangulation the cord is usually placed lower down, just above, immediately across or just below the thyroid. In hanging, with one exception, the lowest part of the cord is in front, and in each side it passes backward and upward. The exception is when one hangs himself in a horizontal position, especially with his face downward. In strangulation the cord lies nearly or quite horizontally. In hanging the passage of air is prevented by the base of the tongue being carried back against the posterior wall of the pharynx, while the posterior nares are tamponed by the soft palate and the apex of the larynx is carried upward and backward. In strangulation the tongue and soft palate may not be materially affected in position. The exclusion of air is more speedily and completely secured in hanging than in suffocation. In hanging the interruption of the flow of blood is complete; the jugular veins, the carotid and vertebral arteries are all occluded. In strangulation the veins are soon occluded, the carotids slowly and often only partially, while the vertebral arteries are never closed. The insult to the vagus center through the superior laryngeal may be the same in hanging and in cord strangulation. The phenomena of death are much the same in the two, but they proceed more slowly in strangulation, the stage of dyspnea is prolonged, consciousness is not so quickly lost and death is not so sudden. When the cord is placed across the thyroid, much force is necessary and in the majority of instances the arrest of the air stream is not complete. The vertebral arteries still carry some oxygenated blood into the brain and consequently the arrest of brain function is not so abrupt as it is in hanging. With the flow of blood into the brain only partially arrested while the return is wholly stopped, engorgement of this organ necessarily follows. It must not be inferred from the above that death cannot be speedily induced by strangulation, and it is only by comparison that the death agony can be said to be prolonged. In death by hanging the loss of consciousness is instantaneous, in the more violent forms of strangulation it may be measured in seconds, but, under ordinary conditions, in minutes.

The postmortem appearances after death from cord strangulation usually differ quite markedly from those observed in hanging. Externally there is venous

engorgement of the scalp and face, and, in short, of every part above the cord. The cord grooves or marks may be one or more, depending upon the number of times the cord has been brought about the neck. These may be narrow and deep or broad and superficial depending upon the nature of the cord and the degree of force applied. As has been stated the cord grooves lie lower than in hanging and pass around the neck horizontally. Usually the track of the cord can be traced wholly around the neck, over the back as well as along the throat. Since the body is not suspended hypostatic ecchymoses so prominently seen on the dependent portions of the suspended corpse are lacking or are to be found on the back if the corpse has been for some hours in a supine position.

According to Reuter[1] there are two groups of marked blood extravasations quite generally present after death from cord strangulation. The first is in the neighborhood of the strangulation groove, generally above it, and consists of hemorrhages in the cervical muscles, their sheaths, the intermuscular tissue, the capsule of the thyroid and under the perichondrium of the laryngeal cartilages. These are supposed to be due to the direct pressure of the cord. The second group is quite removed from the line of the cord and is distributed at points of greatest congestion, as near the angle of the lower jaw, in the floor of the mouth, in the tonsils, and in the connective tissue behind the trachea. Fracture of the laryngeal hyoid framework is not frequent, but one may find fracture of the thyroid and annular cartilages, less frequently of the arch of the hyoid bone. Seldom hemorrhage into the sheaths of the blood vessels is found and rupture of the intima has been reported only once (Ziemke).

On dissection, congestion is prominent, especially in the brain and soft parts of the skull; moreover, the mucous membrane of the pharynx, the base of the tongue and the esophagus is congested and often shows numerous ecchymoses. Sometimes the surface of the trachea is covered with a white or blood-stained foam that results from a pulmonary edema due to the prolonged dyspnea.

It seems to be generally believed that suicide by strangulation with a cord is a difficult feat, and it is true that the majority of deaths from this cause are not self-inflicted. However, the number of suicides in this manner, while less than the number of murders, makes up from 20 to 30 per cent of the total deaths from this cause, and possibly if the strangulation of the newly born be excepted, the percentage of suicides is larger. The courage and resolution displayed by the suicide in this direction are quite remarkable, even the use of a stick to make the pressure greater by twisting the cord has been resorted to not only in murder but in suicide. A case is reported in which a woman used her own hair to strangle herself. It will be seen that the question between suicide and murder is not always an easy one. The strangulation of young children in this manner is either homicidal or accidental, generally the former. In adults it may be suicide or murder, more frequently the latter. In twenty-two cases reported by Reuter, seven were suicide. The kind of knot has in two instances at least given a clue to the hand that tied it. In one of them Tardieu recognized the knot as one used by artillerymen and this led to the arrest of the right man; in another the knot was that employed in a factory where shawls were made and this enabled Hofmann to show that it was suicide. In murder the vio-

lence of the act is generally greater and death more speedy. On account of the greater violence more local injury is done and this shows itself in more frequent fractures. On account of the more speedy death the cyanosis of the face and the congestion of the scalp, soft parts of the skull and the brain is less marked in murder than in suicide. In murder, especially when the victim is an adult, other injuries are often done, such as those that result from blows on the head and stab wounds of the chest. However caution must be exercised here for the desperate man intent on suicide may wound and bruise himself severely before completing his task by strangulation. The marks upon children when killed by strangulation are often slight compared with those seen in adults. This follows from the helplessness of the victim, the feeble efforts made to free itself, the softness of the tissue, the use of a broad cord, and especially to the fact that suffocation is often combined with strangulation.

Accidental death by cord strangulation may happen and some interesting cases have been reported. Smith tells of a boy who was accustomed to carry a weight suspended about his neck. One day he was found dead in his chair; the weight had fallen pulling the cord tight about his throat. Taylor reports the case of a girl who was carrying a heavy basket suspended from her shoulders to market. She climbed onto a wall and sat down to rest, the basket fell behind her pulling the cord about her throat and strangling her to death.

The differentiation between hanging and cord strangulation is usually easily made by the direction of the cord groove, as has already been pointed out, but when one hangs himself while lying on his face, in which case the lines will be horizontal and if the rope has been twice passed about the neck the groove may extend all the way around.

Reuter formulates the following as typical evidences of death by cord strangulation:

1. Cyanosis of the face with or without ecchymoses.
2. Numerous ecchymoses on the lids and conjunctiva.
3. Congestion of the scalp, brain and the meninges.
4. Hemorrhages in the soft tissues of the throat, which lie either near or above the strangulation grooves and in the sheaths of the cervical muscles, in the intermuscular connective tissue, and under the perichondrium of the laryngeal cartilages, or removed from the strangulation groove and near the angle of the lower jaw, in the floor of the mouth, in the tonsils and in the mucous membrane of the pharynx.
5. Marked injection of the mucous membrane of the upper air passages together with numerous small ecchymoses.

Strangulation with the Hand.—When the larynx is seized laterally between the thumb and fingers, as has been shown by the investigations of Langreuter,[2] it is easily compressed, much more readily than when the pressure is directly backwards. This lateral pressure is the most efficient agent in the causation of death by strangulation with the hand. In fact, however, the pressure is generally not exclusively from the sides but at the same time upwards and backwards. Theoretically the ends of the fingers and thumb are in position in this act to compress the large vessels of the neck, but actually this seldom occurs, but it does occur in exceptional instances. Ziemke states that repeatedly in this

form of strangulation in the newly born he has found hemorrhages in the vascular sheaths and in one case he observed rupture of the intima of the right carotid identical with that much more frequently seen in death from hanging. Irritation of the superior laryngeal nerve is more pronounced in this form of violence than in either hanging or in strangulation with a cord. Animal experiments have shown that mechanical irritation of this nerve may cause sudden arrest of either the heart or the respiratory movements. Hofmann observed like effects on compressing with his fingers the larynx of a tracheotomized dog. Indeed, he found that a single short compression of the larynx sufficed to temporarily arrest respiration and that continued pressure caused dyspnea to follow the temporary arrest. Indeed pressure or other injury to the larynx may cause death through the nerves without closure of the windpipe. Brouardel tells of a girl being killed by a light blow on the larynx and he speaks of this as an instance of laryngeal shock. However, death is seldom due to nervous insult only and fracture of the laryngeal cartilages occurs in most instances of death from strangulation with the hand. It has been claimed that death has resulted from merely grasping a man by the larynx but in these instances it is more than probable that the force of the grasp has been underestimated. Fracture of the thyroid is not uncommon and it seems that in the aged this cartilage may become exceedingly brittle. The mechanism of death by strangulation involves in most cases more or less marked injury to the larynx or thyroid with the effect through the nerve and in rare instances compression of the blood vessels. In lateral compression death may be wholly due to occlusion of the air passage.

After death from this form of strangulation the face is cyanotic; there are ecchymoses in the skin and especially in the eyelids and the conjunctiva; marked congestion of the scalp, soft parts of the skull, the brain and the meninges; there are also ecchymoses in the mucous membrane of the air passages and in the viscera.

The most characteristic external effects of this manner of death are seen in the marks left by the finger nails on the throat. As a rule these marks are more numerous on the left side, because on this side are placed the fingers of the assailant provided he be right handed. It must not be supposed that the thumb makes only one mark, or that the fingers always make four and no more. As the assailant tightens his grasp and his thumb and fingers press the soft parts in, the marks made upon either or both sides may be numerous. Moreover, when the victim is strong enough to make any decided resistance there may be scratches over the face and about the throat quite removed from the larynx. Rarely there are marks in those who have met death by hanging or by cord strangulation that may have the appearance of scratches caused by the finger nails. Liman reports a case of this kind in one hanged and on investigation he found that they were due to small buttons on the cord that had been used by the suicide. Scratches with the fingers are not likely to lie in the same plane but are unevenly distributed. The finger marks may be wholly wanting when some article of clothing lies between the hand of the assailant and the throat of the victim and the story is told of a villain who had repeatedly practiced this form of murder and that he always did it with a gloved hand. Brou-

[Continued on p. 7803]